S. HRG. 98-1206

MEDICAL RESEARCH AND ITS IMPACT ON THE NATION'S HEALTH AND ECONOMY

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS
UNITED STATES SENATE

NINETY-EIGHTH CONGRESS

SECOND SESSION

SPECIAL HEARING

Printed for the use of the Committee on Appropriations

U.S. GOVERNMENT PRINTING OFFICE

40-856 O WASHINGTON : 1985

S181-25

COMMITTEE ON APPROPRIATIONS

SUBCOMMITTEE ON DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

LOWELL P. WEICKER, JR., Connecticut, *Chairman*

MARK O. HATFIELD, Oregon	WILLIAM PROXMIRE, Wisconsin
TED STEVENS, Alaska	ROBERT C. BYRD, West Virginia
MARK ANDREWS, North Dakota	ERNEST F. HOLLINGS, South Carolina
WARREN RUDMAN, New Hampshire	THOMAS F. EAGLETON, Missouri
ARLEN SPECTER, Pennsylvania	LAWTON CHILES, Florida
JAMES A. McCLURE, Idaho	QUENTIN N. BURDICK, North Dakota
PETE V. DOMENICI, New Mexico	DANIEL K. INOUYE, Hawaii

Majority Professional Staff

CLAUDIA INGRAM, RIKI POSTER SHEEHAN, CAROL ORTEGA, JAMES SOURWINE, STEVEN BONGARD, and TERRY L. MUILENBURG

Minority Professional Staff

TOM VAN DER VOORT and MARION R. MAYER

Administrative Support

NANCY C. ANDERSON, PATRICIA F. FALSEY, SUSAN A. GORMAN, and BARBARA L. RHODEN

CONTENTS

	Page
Senator Mark O. Hatfield, opening statement	1
Senator Pete Domenici, remarks of	2
Dr. Murray Goldstein, Director, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Department of Health and Human Services, statement of	3
Biographical sketch	4
Dr. Leonard Laster, president, Oregon Health Sciences University, statement of	9
Biographical sketch	14
Prepared statement	10
Dr. Edward Herbert, professor of chemistry, University of Oregon and director, Institute for Advanced Biomedical Research, Oregon Health Sciences University, statement of	29
Biographical sketch	33
Prepared statement	30
Dr. David Kabat, professor of biochemistry, Oregon Health Sciences University, statement of	45
Biographical sketch	
Prepared statement	46
Dr. Edward Neuwelt, associate professor of neurosurgery, assistant professor of biochemistry, Oregon Health Sciences University, statement of	45
Biographical sketch	49
Dr. Richard Hersh, vice president for research, University of Oregon, statement of	64
Biographical sketch	65
Dr. Aaron Novick, director, Institute for Molecular Biology, University of Oregon, statement of	72
Prepared statement	73
Dr. Roderick Capaldi, chairman, Department of Biology, University of Oregon, statement of	72
Biographical sketch	79
Prepared statement	76
Dr. Vaughn Critchlow, director, Oregon Regional Primate Research Center, statement of	88
Biographical sketch	92
Prepared statement	89
Dr. Dwight S. "Pete" Fullerton, professor of medicinal chemistry, Oregon State University, statement of	99
Biographical sketch	106
Prepared statement	100
Dr. Neal H. Barmack, chairman, Good Samaritan Hospital and Medical Center, Neurological Sciences Institute, statement of	113
Biographical sketch	121
Prepared statement	114
Dr. F. Owen Black, director of vestibular clinic, Good Samaritan Hospital and Medical Center, Neurological Sciences Institute, statement of	113
Dr. Lillian M. Pubols, senior scientist, Good Samaritan Hospital and Medical Center, Neurological Sciences Institute, statement of	113
Biographical sketch	122

MEDICAL RESEARCH AND ITS IMPACT ON THE NATION'S HEALTH AND ECONOMY

FRIDAY, AUGUST 24, 1984

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, EDUCATION AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
Portland, OR.

The subcommittee met at 2 p.m., in the Pioneer Courthouse, Portland, OR, Hon. Mark Hatfield, presiding.

Present: Senators Hatfield and Domenici.

NONDEPARTMENTAL WITNESSES

OPENING STATEMENT

Senator HATFIELD. The meeting will please come to order. We're delighted to be conducting an Appropriations Committee hearing in Oregon on the subject of great and ever-growing importance to our State and the Nation—a subject concerning the effective investment in medical research. Primarily through Federal support for the National Institutes of Health, as well as other science agencies, biomedical research has been receiving from the Congress in the recent past a most deserved and stable base of support.

Stability of support is crucial to research. It is important to remember that to maintain the momentum of scientific inquiry, it is important also to attract and retain talented investigators for both this and future generations, because scientific investigations do not always produce immediate results—sometimes no conclusive results whatsoever. Most of the support for medical research cannot be left solely to the private sector nor to the financially hard-pressed academic institutions.

There are many obvious as well as not so obvious reasons why medical research is crucial to our Nation's future and why it is deserving of continued Federal support and expansion. Medical research, for instance, has increased the survival rate of childhood cancer victims from 5 to 57 percent in the last two decades; reduced the death rate from coronary heart disease by 30 percent since 1970, and reduced the death rate from stroke by 46 percent since 1970. There are so many other examples resulting in lower death rates and human suffering.

But medical research has other economic benefits to the overall economy in that it has spawned more than 100 new companies in the emerging biotechnology industry creating $1 billion in private sector investments in the year 1983 alone. It is estimated that research has contributed over $40 billion to the GNP every year from nonhealth related products.

I have long envisioned that the talent and leadership of Oregon would propel our State to becoming one of the Nation's leaders in excellence and scientific research. As I look out over our distinguished witnesses here today, I know that we are achieving that goal.

I am especially pleased to have Senator Pete Domenici of New Mexico joining us today. Senator Domenici is not only an active member of the Appropriations Committee, but he adds a most important dimension to our committee because of his dual role as chairman of the Senate Budget Committee. He manages that committee with great skill and ability—probably one of the most difficult committees in the Senate to maintain course and direction.

And so, Senator Domenici, we welcome you not only to Oregon, but for the role in which you have been so effective in helping in the area of research and development in the biomedical fields. And I would invite you at this time to make any opening remarks you wish. Without objection, I will include my full statement in the record as if given.

REMARKS OF SENATOR DOMENICI

Senator DOMENICI. Thank you very much, Mr. Chairman. I will ask that you make my statement part of the record. I think we have such wonderful witnesses and so little time that I certainly don't want to take very long in my opening remarks.

I want to commend you for calling the hearings. I would say to the people here from Oregon that it's a real pleasure to be here with your Senator and with you. Not too long ago, the chairman and I were discussing the future. Since we're both running, it was all conditional upon positive things happening in November, but at that point we were talking about the next 6 years; and I might say to you that my friend, the chairman, said:

> My 6 years will have as one of its focal points and one of my commitments the continued growth in American research in biomedical areas and all areas of medical research, saying I am convinced that therein lies some real room for achievement in this country, and I'm going to spend a great deal of my time and effort on it.

I told him at that point that I had an abiding commitment in the area of research and science but that I had a growing commitment and concern about one part of our medical research: that which has to do with mental illness. We have sort of formed a pact. I am going to work hard on that one and help him with his, and he's going to lead the way in the area he's interested in; and together we're going to see that we continue with what we've started.

I just would like to say that in these times of frugal spending, in particular let me mention 1985, and thank the chairman for his work. We

are not going to spend less on medical research in 1985; we are going to spend more. And not just a little bit more. We plan to spend $650 million more on NIH and related matters in 1985 over 1984. And that's part of the deal we've struck already with our President. It will fit in the numbers that we've agreed upon, Mr. Chairman. And that will probably accommodate 1,800 new grants to institutions, universities, colleges, and the like, over what we were able to do last year.

I think that's an early start on your commitment that you described to me, and I'm delighted to be a part of it and help you with it and to be here today to hear from the distinguished experts in your State. Thank you very much, Mr. Chairman.

Senator HATFIELD. Thank you, Mr. Chairman and dear friend, Pete Domenici.

STATEMENT OF DR. MURRAY GOLDSTEIN, DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Senator HATFIELD. Our first witness today has traveled from Washington, DC, just specifically to be here at this hearing. Dr. Murray Goldstein is the distinguished Director of the National Institute of Neurological and Communicative Disorders and Stroke. Earlier this year I had the pleasure of listening to Dr. Goldstein on his own turf at the NIH, and a presentation he made at that time was truly most engaging, thrilling, exciting.

Dr. Goldstein has served in his current capacity as Director since 1982, and before that was Acting and Deputy Director of the Institute. There are many who believe that the greatest promise in medical research in the coming years will be in the area of neurological sciences as we seek to unlock the mysteries of the brain, and how the brain functions and how it dysfunctions.

BIOGRAPHICAL SKETCH

I will not try and list all of his credentials because they are so numerous, but Dr. Goldstein's leadership has impressed people not only in the scientific community but in the Congress as well as in the public. Dr. Goldstein will discuss the importance of biomedical research to the Nation and delineate the Federal role in support and conduct of biomedical research. The National Institutes of Health is the focus of the Federal commitment to basic and clinical biomedical research. Dr. Goldstein will summarize highlights of recent accomplishments of NIH-sponsored research and explain how these advances are improving the health of the American people. He will also discuss Alzheimer's disease, a dementia which now strikes almost 2 million older Americans and is a specific disease, not a mere consequence of aging. He will emphasize research leads and opportunities and describe how the National Institutes of Health is capitalizing on these opportunities in the attempt to identify a cure and to prevent this devastating disease.

We will insert your biographical sketch in the record before you proceed.

[The information follows:]

BIOGRAPHY OF MURRAY GOLDSTEIN, D.O., M.P.H.

Position.—Director, National Institute of Neurological and Communicative Disorders and Stroke.

Birthplace and date.—New York, NY; October 13, 1925.

Education.—B.A., New York University, 1947; D.O., Des Moines Still College of Osteopathic Medicine, 1950; and M.P.H., University of California, School of Public Health, 1959.

Experience.—Director, NINCDS, 1982–present; Acting Director, NINCDS, 1981–82; Deputy Director, NINCDS, 1978–81; medical officer, Commissioned Corps, PHS (Assistant Surgeon General), 1953–present; Director, Stroke and Trauma Program, NINCDS, 1976–78; Director, extramural programs, NINCDS, 1961–76; visiting scientist, Mayo Clinic and Graduate School, Rochester, MN, 1967–68; Chief, Special Projects Branch, NINCDS, 1960–61; Assistant Chief, Research Grants Review Branch, DRG, 1959–60; acting chief, section on virus diseases of the CNS, Bureau of Acute Communicable Disease, California State Department of Public Health, 1958; director, Epidemiology and Biometry Training Grant Program, DRG, 1956–58; and Assistant Chief, Grants and Training Branch, NIH, 1953–58.

Association memberships.—American Academy of Neurology; American Association for the Advancement of Science; American Heart Association, Council on Stroke; American Neurological Association; American Osteopathic Association; Association for Research in Nervous and Mental Disease; member, board of directors, John P. Robarts Research Institute, London, Ontario, Canada (1983–87); Society for Neuroscience; the American Parkinson Disease Association, Medical Advisory Board; Eisenhower Institute for Stroke Research; United Cerebral Palsy Research and Educational Foundation Board of Directors; consultant (neurology), Pan American Health Association; consultant, World Health Organization Program on Neurosciences; World Federation of Neurology; International Brain Research Organization; and Commission on Alternative Health Care, U.S. Olympic Council on Sports Medicine.

Special awards, citations, or publications.—Beta Alpha Epsilon, Biology National Honor Society, NYU; Psi Chi, Psychology National Honor Society, NYU; Sigma Alpha, Osteopathic Scholarship National Honor Society, College of Osteopathic Medicine; Delta Omega, Public Health National Honor Society, University of California; Doctor of Science (Hon), Kirskville College of Osteopathic Medicine; Doctor of Laws (Hon), New York Institute of Technology; Certificate of Merit, American Neurological Association; 2nd vice president, American Neurological Association; Silver Star, Purple Heart, U.S. Army; Meritorious Service Medal, Public Health Service; Distinguished Service Medal, U.S. Public Health Service; Founders Day Medal (S.S. Still Medal), University of Osteopathic Medicine and Health Sciences, Des Moines, IA; associate editor, Stroke, A Journal of Cerebral Circulation, American Heart Association; editorial board, Osteopathic Annals; editorial board, International Journal of Neurology; editorial board, the Journal of Neuroepidemiology; and author of over 20 scientific papers and monographs.

Senator HATFIELD. Dr. Goldstein, it's with the greatest of pleasure that we welcome you here today. And thank you again for all of your leadership and your vision and your foresight.

Dr. GOLDSTEIN. Thank you so much, Mr. Chairman and Senator Domenici. On behalf of Dr. James Wyngaarden and the directors of the other 11 research institutes and divisions, we thank you very much for the opportunity of meeting with you again and telling you about the programs of the NIH and the hope and promise that it has for us.

The NIH is truly, truly a child of the Congress. It is part of the administration but a child of the Congress. The leadership that the Congress has taken to see to it that the people of our country have the best and the finest that medical research and medical care can provide is quite obvious. The Senate Appropriations Committee, first chaired by Senator Lester Hill then by Senator Magnuson, and now served by yourself, Senator Hatfield, has been the cornerstone of the opportunity that we have had at NIH.

It would take me perhaps 2 or 3 days to even try to summarize the excitement of the moment in biomedical research, no less the past. As you know, in the field of cancer the conceptualization and finding of the oncogene for the first time gives us the opportunity to understand what cancer really is and how to intervene, and most important, how to prevent. The recent clinical trials run by my colleagues in the Heart and Lung and Blood Institute have given us the first evidence that we can intervene and prevent atherosclerosis, the leading killer probably in our country today.

But perhaps of equal importance—and I must say with my own bias, perhaps of greater importance—is the huge wealth of basic biomedical research that is being supported by all of our units. For out of that raw product comes leadership in science that the United States now has.

I would like to use one example of a bright, new frontier which demonstrates what I'm trying to say, and that's the example of the present excitment and opportunity against a terrible disease that we call Alzheimer's disease, and in the past was called senile dementia. By the way, sir, that's probably the last time I'll ever use the term senile dementia. That's a put-down term. It implies that senility is the end product of aging. It is not. Alzheimer's disease—senile dementia in the past—is a disease. It's a disease of the brain. And because it's a disease, it's preventable and should be treatable.

Not too many years ago we thought that all persons, as they aged, would lose their abilities to think clearly. That's very wrong. Dementia, as I've mentioned, is a disease. It's characterized by extreme forgetfulness, loss of personality, obsessive behavior, and several other losses of intellect.

The loss of memory is probably the most obvious symptom; but it's different from the kind of memory loss that many of us have. I'm getting to the age where I forget where I leave my glasses. But a person who has Alzheimer's disease forgets that they wear glasses. That's the difference. It is a complete eraser or lack of ability to recall an important part of their own life. Not that they forget the names of their children, they forget that they have children. That is what we're talking about.

In 1906 a German physician described in the literature a case of a 51-year-old woman who, over a 4-year period, had degenerated to the point where she had lost her complete personality. She was no longer a person; she was simply living. On her death he examined her brain and found pathological changes in her brain that were then described as

Alzheimer's disease. We thought that was a disease of the younger person—45 to 55—and the book was closed.

About 10 years ago a group of British scientists, working obviously in England, examined brains of a number of people obviously who had died and died of what at that time was called senile dementa, and found that all of the brains were characterized by a severe loss of an important enzyme. That opened up the issue of whether this brain degeneration was due to and was, in fact, a process in biology, the loss of an enzyme. Since then we have learned that that enzyme is very important in the production of what we call a neuro transmitter—acetylcholine.

Nerve cells talk to each other in our brain and through our body; not by sending electrical charges from one to the other, but in fact by sending a chemical message across the space. And one of the most important messengers we call a neuro transmitter is this acetylcholine. And so we've learned in the last 5 years that this important messenger that works in the brain—a neuro transmitter called acetylcholine—is in deficient supply in the brains of persons who have this severe personality loss that we call Alzheimer's disease.

This was an important breakthrough because it told us there was a place where something was going wrong and not just a normal consequence of aging. We then continued to look and a most important finding came about.

I took the privilege of bringing a little poster to show you. Sir, this is a cross section of the brain if we were to cut it this way [indicating] and looked at its side. We know that the brain of people as we age gets smaller, due to a loss of cells and due to a loss of fluid within the brain. But what we did learn is that in all cases of people who had this disease—in all cases—there was a little special area deep in the brain, a nucleus of the brain, which degenerated.

That nucleus has the unique property of sending tracks to all parts of the brain and supplying it with acetylcholine. And so now we have a lead that this is not a disease of the entire brain but a disease which originates in a specified area of the brain. The next step in the puzzle has been brought to our attention.

Senator DOMENICI. Doctor, you said 10 years ago something was discovered. How was it discovered?

Dr. GOLDSTEIN. It was discovered in autopsies of brains of persons. And when the entire brain—and particularly this area of the brain that has to do with intelligence and memory—was analyzed chemically, it was found that the enzyme which produces acetylcholine was in low command, low supply. The next step was to discover that acetylcholine was in low supply.

The third step in my story is: We found that the place that produces the acetylcholine was now falling apart—degenerating.

What I'm trying to do is weave a step-by-step story of progress, and most of this is now within the last decade. What I'm going to tell you now is within the last 2 or 3 years.

One of the problems we have always had in brain research is how do you study the human brain in the living person without injuring that living person. Opening up the skull and taking sections of brain, I would say, is a little invasive. It's a difficult field. Now new methodologies have come to us that are called brain imaging.

You've heard, I'm sure, of the most popular form or the most prevalent use, and that's the CAT scanner, which is a form of x ray using computer technology. This x ray permits us to get pictures of the brain we've never seen before. But, sir, it tells us only about the anatomy of the brain—only about its anatomy, not its functioning.

I could take a CAT scan of a person who has been dead about 2 minutes and you couldn't tell that was a dead person because the anatomy of the brain would still be perfect.

But we have developed a new technology that is now being used in 10 centers around this country that we call PET scanning—positron emission. And what that scanning does in the living human brain is permit us to watch the brain at work, because what we're watching is the brain burn glucose.

The reason for my telling you this story—and I could go on for a while—but the real reason is it's now been applied to Alzheimer's disease. And what we've been able to do is take the living brain of a person who has Alzheimer's disease and watch that brain work.

This, sir, is a PET scan of a person who has Alzheimer's disease [indicating]. This is a prominent woman in Washington, a well-known hostess, who was an expert in giving parties. She can't remember now where to put the knife and fork on the table. She knows how to use the knife and fork but she can't put it on the table. She can choose her clothes from her closet; the colors, the coordination is perfect. But when she tries to get into them she can't. She puts the blouse over her head and gets lost inside the blouse. She's lost the complete concept of space. That's her memory loss.

As you can see here, in a normal brain [indicating] it's not important that there is a nice rounded area of red and yellow. That shows that the brain is working and burning glucose. In this patient you can see the black hole. That does not show up on x ray. And what I'm showing you here is this section of her brain had stopped working, even though its anatomy appears to be fine. And in that area of her brain there's no acetylcholine.

And so, sir, we're at the process now of being able to focus down on a specific area of brain disorder that characterizes this disease and allows us now to begin to target our shots.

The final thing I want to tell you about this is I wish I could say that this was an endeavor solely of the Neurological Institute. But this is an example where NIH does pull together with our colleagues in NIMH. It is a three institute endeavor. The National Institute of Mental Health, National Institute of Aging, and the Neurological Disease Institute are all working jointly. And the results I've been telling you about are the results of our joint endeavor and not of any one activity. So here again

is an example of biomedical science working together and hopefully—hopefully giving us the opportunity to relieve our citizenry, and particularly those of advanced age, of the horror of the thought of losing themselves and not being identified to their loved ones.

Thank you for the opportunity, sir; and I would be delighted to answer any questions I can.

Senator HATFIELD. Thank you very much, Dr. Goldstein, for your most intriguing and enlightening comments. Chairman Domenici, do you have any questions you would like to ask?

Senator DOMENICI. I have one, but it's of a general nature. Doctor, one of the most frequent complaints that I get which I think evidences a basic misunderstanding on the part of nonscientists, is that many of our NIH scientists appear to be very free in terms of what they're doing. Some want them to be more direct, more specific. Can you talk just for a couple of minutes on the record about that concept?

Dr. GOLDSTEIN. Surely, sir. I know exactly what you're saying. There are two methods of approach to biomedical research. One is what we call investigator initiated, and the other one is targeted. The NIH is proud of the fact that about 70 percent of its endeavor is investigator initiated.

Senator Domenici, I am just not smart enough to be able to tell what particular piece of research to go after. Quite frankly, if I knew I'd do it myself. And so 70 percent of our endeavor is to say to the scientific community what is the most scientifically excellent area; what are the opportunities; share them with us.

Out of that group we then choose what we consider from the viewpoint of scientific excellence and potential, those areas which are most worthy of Federal support, funds from our Federal treasury.

The other 30 percent of our endeavor is targeted, where we recognize there is now an opportunity to move ahead rapidly and conclusively. And under those conditions we in the Federal establishment advertise and say, this is what we want done; please come and describe to us how you would do it. Very often supported by contract, but not necessarily.

The study I told you about, in terms of the prevention of atherosclerosis through cholesterol control, was such an effort. And so, sir, the concern of our constituency in public is real. There's no question about that. The only thing I can assure you of is that it requires a balance between the two. The more we know about a disease, the more targeted we can get. But when we take a disease like Alzheimer's, which we didn't know anything about, we had to go to the scientific community and ask them to share their ideas with us; and that's the investigator initiated project.

Senator DOMENICI. Thank you very much, Mr. Chairman.

Senator HATFIELD. Thank you again, Dr. Goldstein, for your long trek to the West. We hope that you will have an opportunity to enjoy our State, at least for a while, before you have to return to that humid, hot, and uncomfortable Washington.

Dr. GOLDSTEIN. Thank you, sir. I had the privilege of spending the morning at your university medical center, and I think I'm going back having learned more than I contributed. Thank you again, sir.

Senator HATFIELD. Thank you very much.

I'm going to ask at this point that the full vitae of each of our witnesses be incorporated in the record at the time of their testimony; and in order to expedite the timeframe, I'm going to avoid trying to list the vitae or the distinguished careers that each one of our witnesses represent.

STATEMENT OF DR. LEONARD LASTER, PRESIDENT, OREGON HEALTH SCIENCES UNIVERSITY

PREPARED STATEMENT

Senator HATFIELD. I would like at this time though to invite a gentleman, Senator Domenici, that I've referred to as one of Oregon's great treasures. In our political context, people think he's a candidate for the office of State treasurer when I say that oftentimes; but I really mean that one of the great treasures of our State is Dr. Leonard Laster, who has been here for 6 years as the president of the Oregon Health Science University and has infused new life into the health science center complex on Marquam Hill; and we're very proud of his work. He is what I would call a true visionary in academia; and yet within that vision that he often shares with us are the pragmatics and the realism that gives it a unique combination in one person.

And so, Dr. Laster, we'll include all your achievements in the record at this point. We are happy to have you here and for me to be able to present Chairman Domenici to one of our fine citizens of Oregon.

[The statement follows:]

STATEMENT OF DR. LEONARD LASTER

Mr. Chairman and members of the committee, it is a genuine pleasure and a distinct privilege to have this opportunity to share with you a few comments on the future directions of biomedicine in this country and on the role that I see for the Oregon Health Sciences University locally and nationally.

As you all know far better than I, this is a period of profound and rapid change in our country's history and both the science and the craft of the healing arts namely, medicine, dentistry and nursing, are privileged to share in this massive tide of growth and metamorphosis. As holds true for the world at large, great adventures and great progress lie before us if we can manage to survive this period of stress and change.

The scientific basis of biomedicine is evolving with ever increasing speed to the point at which biological processes and the disruptions to which they are vulnerable, as well as the diseases that arise from such disruptions, will be understood more thoroughly and more completely at the level of individual chemical molecules. This understanding is emerging by means of the powerful discipline of molecular biology and more than ever, I believe, such understanding carries with it the promise of the ability to develop highly targeted and extraordinarily effective means for the prevention and cure of human disease. In no disciplines is the progress more vigorious and more challenging than in neurobiology, the study of the brain and the nervous system, and in oncology, the study of the mechanisms by which normal cells become cancerous. Thanks to a major local philanthropic benefaction and thanks to an expression of confidence by the Congress, encouraged by Senator Hatfield, the Oregon Health Sciences University has been afforded an opportunity to play a major role in the development of molecular biology, of neuroscience and, more generally, of molecular medicine.

The Oregon Health Sciences University is one of the country's sixteen free standing academic health centers, it includes three schools - medicine, dentistry and nursing, a University Hospital, Crippled Children's Center, a Dental Clinic, and, when it is completed in 1986, an Institute for Advanced

Biomedical Research that will focus on molecular biology and neuroscience. The University is closely tied to a Regional Primate Research Center, a Veterans Administration Medical Center now being rebuilt, and a Shriner's Hospital. The Health Sciences University is one of the eight component units of the Oregon State System of Higher Education. Twenty seven percent of its annual budget of approximately 180 million dollars is derived from the state's general fund.

The University's programs date back almost 100 years. Its component institutions enjoy a record of distinguished accomplishment in their capacity to produce well trained clinicians in each of the three major schools and in a number of special accomplishments. It was at the Oregon Health Sciences University that the first artifical valve was developed for implantation in a human heart as a substitute for a diseased valve. It was at the Health Sciences University that for the first time a catheter with a ballon tip was threaded through a blood vessel to the point where an obstruction was threatening the viability of a patient's leg. By opening up the obstruction the patient was saved the stress and tragedy of amputation. This began what is now called interventional radiography, a new and burgeoning discipline in the care of human beings.

Currently the Nursing School enjoys the position of major leadership in the country in the evoluation of nursing as a scientific as well as academic discipline. The Dental School enjoys an outstanding reputation as a training ground for accomplished clinicians. The School of Medicine is at the forefront of a number of areas including studies on the development of heart disease, by virtue of the disposition of fatty material in the blood vessels that supply the heart muscle, as well as areas of molecular biology and neuroscience. In just a moment or two you will hear from two of our many leaders. Dr. Neuwelt has developed the means of opening up the access to the human brain so as to treat cancers and infections in the brain that were hitherto unreachable in adequate quantity by therapeutic drugs injected into the blood stream. Dr. Kabat's work on the basic mechanisms in the development of cancer is contributing significantly to our progress in this field. These

are but two of many investigators in the School of Medicine who are helping to bring a new era to existence.

The Health Sciences University is undergoing a major renaissance in addition to the opportunity to take part in advances in molecular neurobiology. Again, thanks to the Congress and Senator Hatfield we are developing a center for the application of the growing field of imformational science to the provision of medical care. A number of chairs have been established: one in heart research, one in neurological research and there are more to come. The plan for the future of the University is summarized in the diagram I have attached to my prepared statement. If I may direct your attention to that diagram, the first line makes it clear that our primary goal is education, but the type of education we give in this institution cannot take place without patient care and research all based on a commitment to excellence and humanitarian principles. The short term goals include surviving this period of ecomonic difficult, in Oregon in particular, and strengthening our hospital care programs so as to provide caring attention to patients based on high skill, good science and on a deep concern for the cost effectiveness of health care in hospitals. We are hoping, in particular, to combine the efforts of our three schools in a concern for the care of the aged patient, and to examine whether or not the hospital setting that we provide to aged individuals can be improved to inhance their self-sufficency when their diseases are treated.

On the line labeled intermediate goals, we indicate our intention to assess the quality of our graduates, their concern for the highest principles of the art as well as the sciences of the healing disciplines, and to take such steps as seem logical to heighten their sensitivity to the human aspects of their professions. We hope to bring the several disciplines that are incompassed within our University into some institutional coherence so that we can envision the time when nursing, dental and medical students all study together about the care of the cancer patient, the care of the aged patient or the cost of health care. We also take very seriously our regional responsibilities and we are beginning a Ph.D. program in nursing to provide

the leadership for the schools of nursing locally and nationally as well as to strengthen our research in the field of nursing, especially as it relates to the behavioral aspects of the health care.

The last section represents a continuum of efforts in molecular biology and our new institute. We also hope, through the new chairs of research that we are establishing, to be able to take the information from the laboratories to the bedside expeditiously, in our center for technology and medicine we hope to develop new approaches to the care of patients and to focus on their cost effectiveness. Society has become too irritated with technology and attributes to it the high cost of health care and becomes increasingly prone to decide to ration the use of technology. The answer is not so much rationing as lowering the cost of technology to make it available to all who need it. We also hope to develop a group that will be able to help industry and national organizations in their efforts to maintain the quality of health care while lowering its cost. Our information systems center will in time, we hope, bring the latest information to health practitioners at the outskirts of our societal systems and thereby improve both the quality and cost effectiveness of the care they deliver.

The Oregon Health Sciences University is a major force for economic development in Portland and in Oregon. It is the fifth largest employer in this city. Its annual budget, $180, when inhanced by an conservative economic mutiplier of 2.5, accounts for some $400 to 500 million of economic activity in this area. In the past few years construction related to the Health Sciences University has included $150 for the Veterans Adminstration Medical Center; $20 for the Institute for the Advanced Biomedical Research; $10 for the Shriner's Hospital; and in time, $15 for the Biomedical Information Communication Center. It is not unreasonable to expect that new businesses will evolve around our work in molecular biology, technology and information systems all to the benefit to the local area and the country as a whole.

In conclusion, I would state that when I went to medical school the concept of genetics was purely a paper concept. You could not taste, feel or

see a gene. Today individuals such as our next speaker are able to cut a gene out of a human cell, put it in a bacterial cell and have it make such rare and valuable material as human growth hormone. It has been shown that there are some eight genes in human cells, which after they have done their work in infancy become dormant, but under special circumstances are reawakened and encourage abnormal cell division. These genes are called oncogenes or cancer genes. It is not unrealistic to expect that as our understanding of oncogenes evolves, an approach to treatment of cancer will evolve with it. The human being is subject to almost 1000 inherited diseases of the body chemistry, each due to a defective gene. It is not unrealistic to envision a time when molecular biology will allow a correction of some of the genetic defects involved in these diseases. I could go on and on. I would simply state that one of the individuals whose work has contributed significantly to the hope and excitement of molecular biology and genetics and neuroscience is Dr. Ed Herbert and it gives me great pleasure to introduce him to you at this time.

Biography of Dr. Leonard Laster

ADDRESS: Office
Oregon Health Sciences University
3181 S.W. Sam Jackson Park Road
Portland, Oregon 97201

Home
1863 S.W. Montgomery Drive
Portland, Oregon 97201

BIRTH: August 24, 1928
New York, New York

FAMILY: Married: Ruth Ann Leventhal, December 16, 1956
Children: Judith Eve, November 20, 1959
Susan Beth, April 13, 1962
Stephen Jay, January 15, 1965

EDUCATION:
(Degrees) A.B., Harvard College, 1949, Biochemical Sciences (magna cum laude), attended 1944-46 and summers of 1947 and 1948.
M.D., Harvard Medical School, 1950.

(Honors) Edwards Whitaker Prize for outstanding freshman, Harvard College, 1944.
Phi Beta Kappa, Junior Year, Harvard College, 1945.
Edward Austin Fellowship, Harvard Medical School, 1947-50.
Alpha Omega Alpha, Harvard Medical School, 1949.

TRAINING:

1950-53:	Intern, Assistant Resident, Resident, Medical Service, Massachusetts General Hospital, Boston, Mass.
1958-59:	Fellow, Gastroenterology, with Dr. Franz J. Ingelfinger, Massachusetts General Hospitals, Boston, Mass.

QUALIFYING EXAMINATIONS:

National Board of Medical Examiners, Diplomate, July 23, 1951, Certificate No. 23673.
American Board of Internal Medicine, Internal Medicine, November 9, 1961, Number 18691.
American Board of Internal Medicine, Gastroenterology, March 19, 1966, Number 18691.
Registration, to practice medicine, Massachusetts, May 22, 1952, Certificate No. 23047.
Registration, to practice medicine, New York, December 23, 1977, Certificate No. 133336.
Registration, to practice medicine, Oregon, October 13, 1978, Certificate No. 16005.

PROFESSIONAL POSITIONS:

Oregon Health Sciences University, Portland, Oregon

1978-	President
1978-	Oregon Regional Primate Research Center, Principal Investigator, ex officio.

Downstate Medical Center, State University of New York, Brooklyn, N. Y.

1974-78:	Vice-President for Academic and Clinical Affairs and Dean, College of Medicine.
1976-77:	Acting President (during President's sabbatical leave, October 1976 to March 1977).

National Academy of Sciences - National Research Council, Washington, D.C.

1973-74:	Executive Director, Assembly of Life Sciences and Division of Medical Sciences.

Executive Office of the President, Washington, D. C.

1971-73:	Assistant Director for Human Resources, President's Office of Science and Technology.
1969-71:	Special Assistant (to President's Science Adviser), President's Office of Science and Technology (on detail from National Institutes of Health).

National Institute of Arthritis, Metabolic and Digestive Diseases, National Institutes of Health, Bethesda, Md.

1969-73:	Chief, Digestive and Hereditary Diseases Branch.
1965-69:	Chief, Section on Gastroenterology.
1959-65:	Chief, Gastroenterology Unit.
1954-58:	Senior Investigator, Metabolic Diseases Section.

ACADEMIC APPOINTMENTS:

1978-	Professor of Medicine, School of Medicine, Oregon Health Sciences University, Portland, Oregon
1974-78:	Professor of Medicine, Downstate College of Medicine, State University of New York, Brooklyn, N.Y.
1966-74:	Professorial Lecture in Physiology, George Washington University School of Medicine, Washington, D. C.

	1956-58:	Visiting Physician, District of Columbia General Hospital, George Washington University Service, Washington, D. C.
	1954-58:	Associate in Medicine, George Washington University School of Medicine, Washington, D. C.
	1953-54:	Visiting Investigator, Laboratory of Dr. DeWitt Stetten, Jr., Public Health Research Institute.
	1952-53:	Teaching Fellow in Medicine, Harvard Medical School, Boston, Mass.

ADDITIONAL PROFESSIONAL ACTIVITIES:

Marine Biological Laboratory, Woods Hole, Mass.
Laboratory Investigator, summers, 1962-69.
Library reader, summers, 1973-76.
Organized and chaired Symposia on National Policy and the Biomedical Sciences, summers of 1971 and 1972.

MILITARY RECORD:

1952-73: Commissioned Corps, United States Public Health Service, active duty, final rank Assistant Surgeon General (Rear Admiral).

ORGANIZATIONS, PROFESSIONAL: (Active)

American Association for the Study of Liver Diseases
American College of Physicians
American Federation for Clinical Research
American Gastroenterological Association
American Society of Biological Chemists
American Society for Clinical Investigation, emeritus
Association of American Medical Colleges
Harvey Society of New York
Marine Biological Laboratory Corporation, Woods Hole, Mass.
Multnomah County Medical Society, Portland, Ore., Board of Trustees
Oregon Medical Association
Sigma Xi
Portland Academy of Medicine

ORGANIZATIONS, PROFESSIONAL: (Past)

Council of Deans, Association of American Medical Colleges, 1974-78.
Diagnosis Research Advisory Group, National Cancer Institute, National Institutes of Health, 19 -81.
Eastern Gut Club, resigned 1969.
Foundation for Advanced Education in the Sciences, Inc., Bethesda, Md., Board of Directors, 1965-69, and Secretary, 1967-69.
National Halothane Study Subcommittee, Committee on Anesthesia, Division of Medical Sciences, National Academy of Sciences - National Research Council, 1964-67.
William Earl Clark Society of Clinical Gastroenterology, Washington, D. C., resigned 1969.

CIVIC ORGANIZATIONS: (Active)

Boys Scouts of America, Columbia Pacific Council, Advisory Board
City Club of Portland, Member
Medical Research Foundation of Oregon, Board of Directors
Oregon Contemporary Theater, Board of Directors
Oregon Symphony Association, Board of Directors and Past Chairman of Long Range Planning Committee
Portland Chamber of Commerce, Board of Directors
Rotary Club of Portland, Member
United Way of Columbia Willamette, Board of Directors

CIVIC ORGANIZATIONS: (Past)	Blue Cross of Oregon, Board of Directors, 1978-79. Burning Tree Elementary School, Bethesda, Md., President, Parent-Teachers Association, 1972-73. Family Practice Center, Bedford Stuyvesant Restoration Corporation, Brooklyn N.Y., Board of Directors, 1975-78. Marine Biological Laboratory Club, Woods Hole, Mass., President, 1976-77.
CORPORATE ORGANIZATIONS:	Board of Directors Standard Insurance Company Budget Committee Tektronix, Incorporated Audit Committee Outside Member, Corporate Technology Council Consultant Pharmaceutical corporation: research and development management Paper products corporation: research and development strategy and health care organization
CLUBS:	Arlington Club, Portland, Ore. Cosmos Club, Washington, D. C. Harvard Club, New York, N.Y. University Club, Portland, Ore.
JOURNAL: (Active)	Biochemical Medicine, Editorial Board
JOURNALS: (Past)	American Journal of Digestive Diseases, Editorial Board Gastroenterology Abstracts and Citations, Editorial Advisor Medical Annals of the District of Columbia, Consulting Editor
CITATION:	Who's Who in America

Bibliography

1. Laster, L., and Muller, A.F.: Uric acid production in a case of myeloid metaplasia associated with gouty arthritis, studied with N^{15}-labeled glycine. Amer. J. Med. 15: 857-861, 1953.

2. Seegmiller, J.E., Laster, L., and Stetten, DeW., Jr.: Incorporation of 4-amino-5-imidazolecarboxamide-4-C^{13} into uric acid in the normal human. J. Biol. Chem. 216: 653-662, 1955.

3. Seegmiller, J.E., Stetten, DeW., Jr., Laster, L., Sokoloff, L., Bunim, J.J., and Wyngaarden, J.B.: Metabolic and clinical aspects of gout. Amer. J. Med. 22: 807-824, 1957.

4. Stetten, DeW., Jr., Talbott, J.H., Seegmiller, J.E., Wyngaarden, J.B., and Laster, L.: The pathogenesis of gout. Metabolism 6: 88-91, 1957.

5. Bunim, J.J., McGuire, J.S., Jr., Hilbish, T.F., Laster, L., La Du, B.N., Jr., and Seegmiller, J.E.: Alcaptonuria: Clinical Staff Conference at the National Institutes of Health. Ann. Intern. Med. 47: 1210-1224, 1957.

6. La Du, B.N., Zannoni, V.G., Laster, L., and Seegmiller, J.E.: The nature of the defect in tyrosine metabolism in alcaptonuria. J. Biol. Chem. 230: 251-260, 1958.

7. La Du, B.N., Seegmiller, J.E., Laster, L., and Zannoni, V.: Alcaptonuria and ochronotic arthritis. Bull. Rheum. Dis. 8: 163-164, 1958.

8. Seegmiller, J.E., Laster, L., and Liddle, L.V.: Failure to detect consistent overincorporation of glycine-1-C^{14} into uric acid in primary gout. Metabolism 7: 376-377, 1958.

9. Seegmiller, J.E., and Laster, L.: The metabolic origin of uric acid. In: Progress in Arthritis. New York, Grune and Stratton, 1958, p. 341-351.

10. Wyngaarden, J.B., Seegmiller, J.E., Laster, L., and Blair, A.E.: Utilization of hypoxanthine, adenine and 4-amino-5-imidazolecarboxamide for uric acid synthesis in man. Metabolism 8: 455-464, 1959.

11. Liddle, L., Seegmiller, J.E., and Laster, L.: The enzymatic spectrophotometric method for determination of uric acid. J. Lab. Clin. Med. 54: 903-913, 1959.

12. Seegmiller, J.E., Zannoni, V.G., Laster, L., and La Du, B.N.: An enzymatic spectrophotometric method for the determination of homogentisic acid in plasma and urine. J. Biol. Chem. 236: 774-777, 1961.

13. Seegmiller, J.E., Grayzel, A.I., Laster, L., and Liddle, L.: Uric acid production in gout. J. Clin. Invest. 40: 1304-1314, 1961.

14. Laster, L., and Ingelfinger, F.J.: Intestinal absorption. Aspects of structure, function and disease of the small-intestine mucosa. New Engl. J. Med. 264: 1138-1148, 1192-1200, 1246-1253, 1961.

15. Topper, Y.J., Laster, L., and Segal, S.: Galactose metabolism: Phenotypic differences among tissues of a patient with congenital galactosemia. Nature 196: 1006, 1962.

16. Williams, H.E., Johnson, P.L., Fenster, L.F., Laster, L., and Field, J.B.: Intestinal glucose-6-phosphatase in control subjects and relatives of a patient with glycogen storage disease. Metabolism 12: 235-241, 1963.

17. Seegmiller, J.E., Laster, L., and Howell, R.R.: Biochemistry of uric acid and its relation to gout. New Engl. J. Med. 268: 712-716, 764-773, 821-827, 1963.

18. Williams, J.N., Jr., and Laster, L.: Investigation of the use of the albino rat for studying gliadin-induced steatorrhea. Metabolism 12: 467-471, 1963.

19. Laster, L., and Blair, A.: An intestinal phosphorylase for uric acid ribonucleoside. J. Biol. Chem. 238: 3348-3357. 1963.

20. Lutwak, L., Laster, L., Gitelman, H.J., Fox, M., and Whedon, G.D.: Effects of high dietary calcium and phosphorus on calcium, phosphorus, nitrogen and fat metabolism in children. Amer. J. Clin. Nutr. 14: 76-82, 1964.

21. Mudd, S.H., Finkelstein, J.D., Irreverre, F., and Laster, L.: Homocystinuria: An enzymatic defect. Science 143: 1443-1445, 1964.

22. Brody, I.A., Wertlake, P.T., and Laster, L.: Causes of intestinal symptoms in primary amyloidosis. Arch. Intern. Med. 113: 512-518, 1964.

23. Waldmann, T.A., and Laster, L.: Abnormalities of albumin metabolism in patients with hypogammaglobulinemia. J. Clin. Invest. 43: 1025-1035, 1964.

24. Fenster, L.F., Buchanan, W.W., Laster, L., and Bunim, J.J.: Studies of pancreatic function in Sjögren's syndrome. Ann. Intern. Med. 61: 498-508, 1964.

25. Finkelstein, J.D., Mudd, S.H., Irreverre, F., and Laster, L.: Homocystinuria due to cystathionine synthetase deficiency: The mode of inheritance. Science 146: 785-787, 1964.

26. Melmon, K.L., Sjoerdsma, A., Oates, J.S., and Laster, L.: Treatment of malabsorption and diarrhea of the carcinoid syndrome with methysergide. Gastroenterology 48: 18-24, 1965.

27. Matthews, D.M., and Laster, L.: Kinetics of intestinal active transport of five neutral amino acids. Amer. J. Physiol. 208: 593-600, 1965.

28. Matthews, D.M., and Laster, L.: Competition for intestinal transport among five neutral amino acids. Amer. J. Physiol. 208: 601-606, 1965.

29. Wolff, S.M., Hathaway, B.E., and Laster, L.: The gastrointestinal system in familial Mediterranean fever. Arch. Intern. Med. 115: 565-568, 1965.

30. Mudd, S.H., Finkelstein, J.D., Irreverre, F., and Laster, L.: Threonine dehydratase activity in humans lacking cystathionine synthase. Biochem. Biophys. Res. Commun. 19: 665-670, 1965.

31. Strittmatter, P., Burch, H.B., and Laster, L.: The appearance of alkaline p-nitrophenyl phosphatase, adenosine triphosphatase and adenosine diphosphatase activities in cilia of developing embryos of Spisula solidissima. Biochem. Biophys. Acta 100: 304-306, 1965.

32. Laster, L., Mudd, S.H., Finkelstein, J.D., and Irreverre, F.: Homocystinuria due to cystathionine synthase deficiency: The metabolism of L-methionine. J. Clin. Invest. 44: 1708-1719, 1965.

33. Matthews, D.M., and Laster, L.: Absorption of protein digestion products. Gut 6: 411-426, 1965.

34. Laster, L., and Waldmann, T.A.: Serum proteins and the gastrointestinal tract. Med. Ann. Distr. of Col. 34: 459-462, 1965.

35. Mudd, S.H., Finkelstein, J.D., Irreverre, F., and Laster, L.: Transsulfuration in mammals: Microassays and tissue distributions of three enzymes of the pathway. J. Biol. Chem. 240: 4382-4392, 1965.

36. Singleton, J.W., and Laster, L.: Biliverdin reductase of guinea pig liver. J. Biol. Chem. 240: 4780-4789, 1965.

37. Laster, L., Spaeth, G.L., Mudd, S.H., and Finkelstein, J.D.: Homocystinuria due to cystathionine synthase deficiency, Combined Clinical Staff Conference at the National Institutes of Health. Ann. Intern. Med. 63: 1117-1142, 1965.

38. Finkelstein, J.D., Mudd, S.H., Irreverre, F., and Laster, L.: Deficiencies of cystathionase and homoserine dehydratase activities in cystathioninuria. Proc. Nat. Acad. Sci. 55: 865-872, 1966.

39. Levy, R.I., Fredrickson, D.S., and Laster, L.: The lipoproteins and lipid transport in abetalipoproteinemia. J. Clin. Invest. 45: 531-541, 1966.

40. Laster, L., Waldmann, T.A., Fenster, L.F., and Singleton, J.W.: Albumin metabolism in patients with Whipple's disease. J. Clin. Invest. 45: 637-644, 1966.

41. Gordon, R.S., Jr., Waldmann, T.A., and Laster, L.: Protein-losing gastroenteropathy. Disease-A-Month, August, 1966.

42. Bunker, J.P., Child, C.G., Davidson, C.S., Gall, E.A., Klatskin, G., Laster, L., Moses, L.E., Mosteller, F., Ngai, S.H., Vandam, L.D., Forrest, W.H., Jr., and Seeley, S.F.: Summary of the National Halothane Study: Possible association between halothane anesthesia and postoperative hepatic necrosis. J. Amer. Med. Assoc. 197: 775-788, 1966.

43. Ockner, R.K., and Laster, L.: Biosynthesis of 7-cholesten-3-ol, Δ5, 7-cholestadien-3β-ol, and Δ5-cholesten-eβ-ol by guinea pig intestinal mucosa in vitro. J. Lipid Res. 7: 750-757, 1966.

44. Mudd, S.H., Laster, L., Finkelstein, J.D., and Irreverre, F.: Studies on homocystinuria. In Himwich, H.E., Kety, S.S., and Smythies, J.R. (Eds.): Amines and Schizophrenia. New York, Pergamon, 1966, pp. 247-256.

45. Warshaw, A.L., Laster, L., and Shulman, N.R.: The stimulation by thrombin of glucose oxidation in human platelets. J. Clin. Invest. 45: 1923-1934, 1966.

46. Waldmann, T.A., Wochner, R.D., Laster, L., and Gordon, R.S., Jr.,: Allergic gastroenteropathy: A cause of excessive gastrointestinal protein loss. New Engl. J. Med. 276: 761-769, 1967.

47. Warshaw, A.L., Laster, L., and Shulman, N.R.: Protein synthesis by human platelets. J. Biol. Chem. 242: 2094-2097, 1967.

48. Brady, R.O., Gal, A.E., Bradley, R.M., Martensson, E., Warshaw, A.L., and Laster, L.: Enzymatic defect in Fabry's disease - Ceramidetrihexosidase deficiency. New Engl. J. Med. 276: 1163-1167, 1967.

49. Mudd, S.H., Irreverre, F., and Laster, L.: Sulfite oxidase deficiency in man: Demonstration of the enzymatic defect. Science 156: 1599-1602, 1967.

50. Irreverre, F., Mudd, S.H., Heizer, W.D., and Laster, L.: Sulfite oxidase deficiency: Studies of a patient with mental retardation, dislocated ocular lenses, and abnormal urinary excretion of S-sulfo-L-cysteine, sulfite, and thiosulfate. Biochem. Med. 1: 187-217, 1967.

51. Warshaw, A.L., Heizer, W.D., and Laster, L.: Pancreatic insufficiency as the presenting feature of hyperparathyroidism. Ann. Intern. Med. 68: 161-167, 1968.

52. Heizer, W.D., Warshaw, A.L., Waldmann, T.A., and Laster, L.: Protein-losing gastroenteropathy and malabsorption associated with factitious diarrhea. Ann. Intern. Med. 68: 839-852, 1968.

53. Danovitch, S.H., Baer, P.N., and Laster, L.: Intestinal alkaline phosphatase activity in familial hypophosphatasia. New Engl. J. Med. 278: 1253-1260, 1968.

54. Weser, E., and Laster, L.: Metabolism of D-xylose and D-xylonic acid in vivo and in vitro by the guinea pig. Biochem. Med. 2: 53-69, 1968.

55. Chase, H.P., Volpe, J.J. and Laster, L.: Transsulfuration in mammals: Fetal and early development of methionine-activating enzyme and its relation to hormonal influences. J. Clin. Invest. 47: 2099-2108, 1968.

56. Laster, L., and Walsh, J.H.: Enzymatic degradation of C-terminal tetrapeptide amide of gastrin by mammalian tissue extracts. Fed. Proceedings 27: 1328-1330, 1968.

57. Percy, A.K., Mudd, S.H., Irreverre, F., and Laster, L.: Sulfite oxidase deficiency: Sulfate esters in tissues and urine. Biochemical Med. 2: 106-117, 1968.

58. Heizer, W.D., and Laster, L.: Peptide hydrolases of the mucosa of human small intestine. J. Clin. Invest. 48: 210-228, 1969.

59. Von Sallmann, L., Gelderman, A.H., and Laster, L.: Ocular histopathologic changes in a case of a-beta-lipoproteinemia (Bassen-Kornzweig syndrome). Documenta Ophthalmologica 26: 431-460, 1969.

60. Heizer, W.D., and Laster, L.: Hydrolases in the mucosa of rat small intestine for phenylalanine-containing dipeptides. Biochem. Biophys. Acta 185: 409-423, 1969.

61. Danovitch, S.H., and Laster, L.: The development of arylsulphatase in the small intestine of the rat. Biochem. J. 114: 343-350, 1969.

62. Tousimis, A.J., Hagerty, J.C., Padden, T.R., and Laster, L.: V. The application of electron probe microanalysis to the study of amino acid transport in the small intestine. In Earle, K.M., and Tousimis, A.J. (Eds.): X-Ray and Electron Probe Analysis in Biomedical Research. Prog. in Analytical Chem. Vol. 3, New York, Plenum Press, 1969, p. 75-85.

63. Volpe, J.J., and Laster, L.: Transsulfuration in primate brain: Regional distribution of methionine-activating enzyme in brain of the Rhesus monkey at various stages of development. J. Neurochemistry 17: 413-424, 1970.

64. Volpe, J.J., and Laster, L.: Transsulfuration in primate brain: Regional distribution of cystathionine synthase, cystathionine and taurine in the brain of the Rhesus monkey at various stages of development. J. Neurochemistry 17: 425-435, 1970.

65. Mudd, S.H., Edwards, W.A., Loeb, P.M., Brown, M.S., and Laster, L.: Homocystinuria due to cystathionine synthase deficiency: the defect of pyridoxine. J. Clin. Invest. 49: 1762-1773, 1970.

66. Volpe, J.J., Lee, C., Laster, L., and Robinson, J.C.: Regional distribution of isozymes of D-amino-acid oxidase and acetylesterase in developing primate brain. Exptl. Neurol. 28: 76-87, 1970.

67. Gardner, J.D., Brown, M.S., and Laster, L.: The columnar epithelial cell of the small intestine: Digestion and transport. New Engl. J. Med. 283: 1196-1202, 1264-1271, 1317-1324, 1970.

68. Laster, L.: Diseases of the small intestine: Malabsorption syndrome. In Keefer, C.S., and Wilkins, R.W., (Eds.): Medicine: Essentials of Clinical Practice. Boston, Little, Brown, 1970, p. 490-495.

69. Loeb, P.M., Strober, W., Falchuk, Z.M., and Laster, L.: Incorporation of ^{14}C-L-leucine into immunoglobulins by jejunal biopsies of patients with celiac sprue and other gastrointestinal diseases. J. Clin. Invest. 50: 559-569, 1971.

70. Laster, L.: The small intestine. Chapter in Metabolic Aspects of Food Safety (Proc. of the Second Food Safety Conference), Oxford, Blackwell Scientific Publications, 1970, pp. 17-36.

71. Volpe, J., and Laster, L.: Transsulfuration in fetal and postnatal mammalian liver and brain. Biology of the Neonate 20: 385-403, 1972.

72. Falchuk, Z.M., Edwards, W.A., Laster, L.: Effect of alpha-aminoisobutyric acid on urinary excretion of homocystine in patients with homocystinuria. Metabolism 22: 605-610, 1973.

73. Warshaw, A.L., and Laster, L.: Protein synthesis by human intestinal mucosa: Variations with Diseases of the Gut. J. Surg. Res. 14: 285-293, 1973.

74. Warshaw, A.L., Waldmann, T.A., and Laster, L.: Protein-losing enteropathy and malabsorption in regional enteritis: Cure by limited ileal resection. Annals Surg. 178: 578-580, 1973.

75. Walsh, J.H., and Laster, L.: Enzymatic deamidation of the C-terminal tetrapeptide amide of gastrin by mammalian tissues. Biochem. Med. 8: 432-439, 1973.

Committee Reports (served as member)

1. The National Halothane Study: A Study of the Possible Association Between Halothane Anesthesia and Postoperative Necrosis. A report of the Subcommittee on the National Halothane Study of the Committee on Anesthesia, Division of Medical Sciences, National Academy of Sciences-National Research Council, 430 pp., 1969.

2. Scientific and Educational Basis for Improving Health. A report of the Panel on Biological and Medical Science of the President's Science Advisory Committee, 66 pp., 1972.

3. Improving Health Care through Research and Development. A report of the Panel of Health Services Research and Development of the President's Science Advisory Committee, 72 pp., 1972.

Representative Talks and Articles

"On Excellence as an Infectious Disease," Alumni Day, Downstate College of Medicine, May, 1975.

"From Bethesda to Brooklyn via the White House," Alumni Day, Harvard Medical School, 1975. Harvard Medical Alumni Bulletin, July/August, 1975.

"Moral and Ethical Imperatives of Science and Medicine: Must We Be Holier Than They?" Convocation Address, Downstate Medical Center, September, 1976.

"Medical Ideas Outstrip Funding for Basic Research," Wall Street Journal, June 15, 1983.

"A Land Where Eagles Dare to Soar," Portland Magazine, July, 1983.

1978-present

More than 50 talks to lay groups and civic organizations and at commencement exercises, such as

- The realities of "excellence"--the view from an academic health center (City Club of Portland, June 2, 1983)
- Quality--the issue in national survival
- Economic development in Oregon
- Immunity to outrage--a danger of our times

Dr. LASTER. Chairman Hatfield, Chairman Domenici, thank you both for the privilege of visiting with you today. For you this may be a routine hearing; for me this is an intensely emotional moment because it exemplifies to me the circularity of life.

I finished my medical training in 1953 in Boston and was invited to come to a new venture in Bethesda, MD, at the National Institute of Health. They were opening something called a clinical center, and I thought I would go for 1 year, and I stayed for some 19. And during the course of those years I saw this country create an enterprise of such superlative excellence, such terrible importance to humanity, I saw nine colleagues go on to win the Nobel Prize in medicine. I saw American medicine changed. We became far from being followers; we became leaders in the entire world; and we contributed to human health beyond all measure.

And the basis for it was not money, was not budgets, but the dedication and caring of the leadership. Senator Hill has been mentioned by Dr. Goldstein. Jim Shannon, who was head of the NIH in those years, is retired and living here in Portland interestingly enough; Representative Fogerty, Senator Magnuson.

And for awhile I was concerned that this commitment to a national battle against disease would follow a pattern of rising to great heights and then being allowed to wither and descend. And one of the reasons for the concern was the lack of champions. And I think with the interest you two are displaying in the substance and in the commitment, there is hope that we will have a resurgence and take advantage of all the excitement that's occurring now.

We are in the midst of a number of revolutions. There's molecular biology; understanding these processes in terms of individual chemical molecules and how they are disrupted in disease states. Neuroscience is burgeoning how the brain works, how communication occurs between one nerve cell and another. Cancer: We're discovering that there are genes in cells which do useful work in the infancy of an organism and then are usually put to sleep. But some factor awakens them in later life and they wake up and tell the cells to divide again more rapidly and make cancers. And you will hear from Dr. Kabat at the medical school here about work on a gene that produces cancer in mice and what he has done with that.

When I was at the NIH we worked on genetic disorders and they were general concepts. Now you can cut out a human gene and transfer it from a human cell to a bacterial cell, and that bacterial cell will now make valuable products such as human growth hormone.

Among the other revolutions that are occuring are a reawakening and a reemphasis of our concern for the humanitarian aspects of medicine. The technology alone is not enough. The caring is being reemphasized and reintroduced. And the two must go hand in hand.

And finally, a concern for the productivity of the enterprise. Are we giving the world effective and efficient care at the lowest possible cost? You are all aware of the concern in that area.

It's a pleasure to be able to say that thanks to your effort, Senator Hatfield, thanks to the Congress, thanks to the tenor of the times, the Health Sciences University here in Portland is being given the opportunity to take part in all these several revolutions. We are the focus and a participant in a network of institutions: The schools on the hill, the Veterans' Administration Hospital that is being rebuilt, the Primate Research Center whose director is here with us today, the Shriner's Hospital studying the molecular biology of collagen—the supporting tissues of the body—the other schools in the State system of higher education, the other hospitals in the city—and you will hear from Good Samaritan Hospital. All of these are forming a network dedicated to moving these areas ahead.

There's a past history of accomplishment here. The first artificial heart valve for implantation in a diseased human heart was created and implanted here in Portland; and an industry grew out of that. Unfortunately, it grew in California. But in the future we hope that the revolution will be more locally tied.

The first person to snake a tube with a balloon on it through a blood vessel to where the blood vessel was obstructed, blow up the balloon and open up that obstruction and thereby save the patient from an amputation, occurred here on the hill; and a whole new field of interventional radiography developed.

Today people are studying in one department a factor in the fat that Eskimo populations eat that seems to prevent the clotting of blood, and, therefore, be a possible means of finding a substance to prevent heart attacks is being studied on the hill.

The programs that are allowing us to take part in this include a new Institute for Advanced Biomedical Research. It began with a local philanthropic gift of $5 million, a $20 million Federal grant, an expression of confidence by the Congress spurred by Senator Hatfield, in the capacity of this institution to take its place with the other, more established institutions in molecular biology. And we're devoting this to molecular biology and brain science. And with this opportunity we've recruited as its director, Dr. Ed Herbert, who will speak to you in a moment.

It will be devoted to understanding all the processes of the type that Dr. Goldstein mentioned at a molecular level. And the premise is that out of the understanding comes the capacity to deal with diseases such as Alzheimer's and other mechanisms of the human brain.

We're also developing a center for biomedical information systems to help with the process of making available to the practicing clinician—nurse, physician, dentist—in all areas of a region, the latest information on a timely basis; and also to spur their capacity to study further and to spur the enjoyment in learning. Because above all, the care of human beings is a knowledge-based activity, and it is 10 percent of the gross national product. And the knowledge industry that grows out of that can be an important one, and we hope that that will spur some economic development as well as the intrinsic value.

The Molecular Biology Institute should be of interest to pharmaceutical organizations and should, in itself, help to spur economic growth.

There's work on depression and the mechanisms of depression, both from the biological and the biochemical point of view, and the cultural point of view. Depression in native Americans is a different phenomenon from depression in others; and our department of psychiatry is working in that area as well.

I won't walk you through it, but attached to the testimony is a vision for the future of the Health Sciences University, and it really is a vision for the future of American biomedicine. I would simply call attention to a short-term goal. We need to improve the way we deliver care. Society is saying, to some degree, we've invested all this money in the research, but I still can't get this or I still have to pay too much for that, or industry is saying we're paying too much. And the response that I'm afraid we're getting is rationing. We will deprive people of opportunities to benefit from the CAT scanners that Dr. Goldstein mentioned, or the NMR scanners. I don't think we can do that. We need to say, how can we lower the cost of making this technology available to people; and we hope to start a center for technology in medicine designed not just to add new technology but to look at the cost factor in making it available.

We need to restore, strengthen, and reinvigorate the humanitarian aspects of health care. One response in society is too many specialists, too many scientists, let's cut back. We don't want to cut back, I believe; we simply want to remind ourselves why we're doing this and to strengthen our commitment to individuals.

We hope, also, to develop the capacity to provide advice and guidance to organizations such as industrial or municipal or State groups on how to not just lower the cost of health care but maintain the quality of it and maintain the effectiveness of it.

These goals are being realized here in Oregon but they're universal throughout the country. In your own State, your academic health center is taking its place as a member of this army; and all of this really is an outgrowth of the commitment through the NIH in particular to belief in the future of this country and a commitment to human health as our highest value. I was concerned until recent days that there are many ideas of scientific excellence that are put forth by younger members of the army of health investigators that go unfunded. The term approved but unfunded became almost a cliche. We cannot afford to throw such wealth on the trash heap of human history; and with the expression of a recommitment of the type that you two have voiced here, I think we will recapture those treasures that we are in danger of losing. And with that I will conclude my testimony and be glad to answer any questions.

Senator HATFIELD. Your full statement, Dr. Laster, will be placed in the record as if read.

Senator DOMENICI. I would have a question, excepting I might ask you first, Mr. Chairman. Is there, in our list, an expert that is somewhat familiar with the choices that bright, young people are making in terms

of where they go. When they get to a point in development, are the best ones becoming medical doctors instead of researchers?

Dr. LASTER. I might take a crack at that.

Senator DOMENICI. Let me ask you that. Somebody contends that as recently as 24 months ago that there was a genuine concern in this country that the very bright young men and women go through college, when they make that final choice a very large percent of them would choose medicine, as such, to become medical doctors and practitioners. Of course we live in a society where there's a very significant emphasis to become materially wealthy, and there's certainly nothing wrong with that. And the side that deals with direct research is not quite as attractive. Do you have any observations with reference to that?

Dr. LASTER. Yes, sir; again, back in 1950 I got out of medical school and the concern was voiced that if you plotted the number of young people in medicine going into research, by 1985, 90 percent of the population would be doing medical research in the country, and there was concern that we were overdoing it. I'm afraid that concern needn't have surfaced because, on the contrary, if you look at a career in biomedicine the uncertainty of the funding, the notion that, I believe, in 1972 of those ideas that were rated as worthy of scientific support, 60 percent would be funded. By 1982 we were down to some 30 percent.

In 1972 we had some 4,500 M.D.'s in training in biomedical research. By 1982 that had dropped to almost 2,000. Some of the factors in it—in addition to the uncertainty of the national commitment—seeing your senior members of the faculty, after a lifetime of work, suddenly finding themselves with good ideas but without funding. And also the economics of it: The average student comes out of medical school today with an indebtedness of some $50,000. Some of the highest tuitions in the country are up $28,000 a year in medical school. Coming out with that kind of an indebtedness to turn to an uncertain career in research is indeed a deterrent. And yet despite this—and this is purely an intuitive feeling—I still think we're getting some of the brightest, most exciting young people both in the Ph.D. and the medical area going into research.

As far as medicine goes as a career, I think nationally at the height we had about five applicants—between five and seven applicants, for each position in medicine in the country, even after we expanded by doubling. Today that has dropped some, and for awhile there was a concern that there was a trend going down; but I think it's leveled off at some 3 or 4 to 1. And I still feel that we are getting our brightest.

The challenge is to get not only the brightest but the most caring; and that is a function not just of the selection process and the role models, but what kind of a society we've become. There was just an article in the New York Times about business leadership becoming more self-concerned, more self-centered, and more inner directed. In a society like that the challenge is to maintain the humanitarian aspect. On the whole, I think we're giving you a very decent product for your national investment.

Senator HATFIELD. I think if I might comment, I think, Senator, that some of our capital as well as our ability to attract such people are people who are here today, like Dr. Goldstein, Dr. Laster, Dr. Herbert, all these others, who in themselves are part of the attraction to keep that process going. It's like any other capital; it's depleted after awhile if we don't take steps to ensure its replication down the road in generations to come. I really feel that's again one of the assets we have with the capital is a professional such as yourself where young people want to come and be with you and be associated with you.

Dr. LASTER. May I supplement that, Senator. In Dr. Herbert's decision to take over the direction of the new institute, he turned down an opportunity, actually, to go to Harvard and have an extremely attractive and important position there, because of the excitement of creating one of the two or three major centers in the country for brain science. With that, we were able to attract as a chairman of anatomy to our school someone who works on the mechanism by which genes make cells divide rapidly when they start a cancer, which is pretty heady stuff for an anatomist to be working on. He came because Dr. Herbert was there.

I believe in short order we will be able to announce the recruitment of a chairman of neurology of superlative quality who undoubtedly will have been influenced by Dr. Herbert.

The other two people you're going to hear from the Health Sciences University, Dr. Kabat, working on the mechanism by which a virus produces cancer in mouse leukemia. He's a true inspiration to the first year medical students with whom he comes in contact. Dr. Neuwelt, working on how to open the brain so that material injected into the blood stream to fight cancer infection can get to where it needs to go in brain disease, is another exciting member of that. He left Texas to come here. And again the work in this institution and in the others that you'll hear from does indeed create the human excitement that is really the basis for the future. And if I may say—and I don't say this in flattery—the kind of interest that you two are evidencing makes a great deal of difference to people who are considering giving their lives to this area. So I thank you on behalf of all of them.

Senator DOMENICI. Thank you very much, Doctor.

STATEMENT OF DR. EDWARD HERBERT, PROFESSOR OF CHEMISTRY, UNIVERSITY OF OREGON AND DIRECTOR, INSTITUTE FOR ADVANCED BIOMEDICAL RESEARCH, OREGON HEALTH SCIENCES UNIVERSITY

PREPARED STATEMENT

Senator HATFIELD. I would like to invite now Dr. Edward Herbert, who has already been introduced by Dr. Laster. Dr. Herbert is professor of chemistry at the University of Oregon and the director—launcher—of the Institute of Advanced Biomedical Research at the Oregon Health Sciences University. Dr. Herbert, we're delighted to have you today. We will insert your full statement in the record at this point.

[The statement follows:]

40-856 O - 85 -- 3

Statement of Dr. Edward Herbert

I. INTRODUCTION

I want to thank Senator Hatfield and this committee for the opportunity to comment on the importance of Biomedical Research to the nation's health and economy. Biomedical research is poised on the verge of a revolution that may be comparable in significance to the harnessing of atomic power in the 30s and 40s. Dramatic discoveries in the biological sciences are leading to a much better understanding of some of mankind's most dreaded diseases including cancer, heart disease and mental disorders. In the next 10 to 15 years the insights generated by these discoveries will provide the means for preventing and curing many diseases and lead to economic dividends by reducing the cost of health care. In the few minutes that I have before you I would like to describe the impact of discoveries in molecular biology on the future course of the health sciences and the practice of medicine.

Molecular biology and its offshoot recombinant DNA research have provided us with powerful new tools for the study of human genetics. We can now separate and analyze the function of the two million or more genes contained in a human cell. This capability will allow us to unravel some of the most intriguing mysteries of human biology such as the blueprint of embryonic development, the ability to communicate and think, and the susceptibility to diseases.

Another development in molecular biology that will have an enormous impact on biomedical research is the ability to alter an organism by transferring specific (cloned) genes from one organism to another. For example, giant mice have been produced by transferring a cloned growth hormone gene from a rat into a mouse embryo. In the next 10 to 20 years this discovery will reshape medicine by providing the technology for correcting specific genetic defects in humans.

II. IMPACT OF MOLECULAR BIOLOGY ON STUDY OF SPECIFIC DISEASES

A. Cancer Research

Molecular Biology has revealed the existence of specific genes that transform normal cells into cancer cells. These genes, called oncogenes, are present in normal cells in an inactive state. They become active when certain viruses or other agents enter the cell. This leads to rapid growth and

invasion of normal tissues resulting in the formation of a tumor. Now that we know which genes are responsible for the formation of cancer cells, it will be possible to identify the products of these genes and to determine how they alter the chemistry of normal cells to cause cancer. It should then be possible to produce very specific agents to prevent the oncogenes from becoming active or their products from altering cell chemistry.

B. Degenerative Diseases of the Nervous System

Recombinant DNA approaches have recently shown that degenerative diseases of the nervous system such as Alzheimer's disease and Huntington's disease have a genetic component. The identification of a specific gene that is defective in Huntington's disease, a 100% fatal disorder, will enable researchers to determine the origin of this disease and identify the defective gene products.

C. Study of Behavior and Treatment of Mental Disorders

Molecular biology and biochemistry have led to dramatic advances in our understanding of brain chemistry and behavior in the past 10 years. A milestone in this field has been the discovery of a vast array of chemicals in the brain that control behavior such as sleep, pain, stress, anxiety, sexual cycles, and learning and memory. These substances (called neuropeptides) are produced in specific pathways in the nervous system. Many drugs that alter behavior such as morphine and valium do so by mimicking the actions of the body's own neuropeptides. Thus, the concept has arisen that for every drug that alters a behavior, there is a natural substance that controls that behavior. For example, the amount of pain we feel is related to the level of the body's own pain killers called enkephalins and endorphins (neuropeptides). This concept is reshaping our thinking about the design of therapeutic agents for modifying behavior and for treating mental disorders such as schizophrenia and depression. If we can understand how genes control the production of specific neuropeptides, perhaps we can intervene in these processes in a much more specific way than drugs we now use. Hence, new agents designed more like the natural ones that the body produces may provide much more effective treatment of mental disorders than is presently possible.

Molecular biology has provided us with tools for isolating the genes that control specific behavior patterns and for determining how they function. Once we understand how these genes work we will be in a position to relate a specific mental disorder to the malfunction of a specific gene or set of genes.

For example, we have an indication that narcotic addiction and withdrawal syndromes and possibly alcoholism involve alteration of the activity of genes that control production of the endorphins and enkephalins.

We are also in a position to understand how genes control learning and memory processes because biomedical scientists have been able to identify specific neuropeptides that are involved in these processes. Aside from providing clues about how the brain works, these discoveries will lay the foundation for understanding mental disorders that are linked to defects in memory and learning such as Alzheimer's disease.

D. Isolation of Peptides that Control Heart Function

Very recently a new class of chemicals (peptides) has been discovered in the heart that controls the action of heart muscle and the flow of blood through the coronary arteries. These substances, called cardionatrins, or cardiac peptides, may be the links that will enable us to understand in much more depth how heart function and blood pressure are regulated. The genes that produce these peptides have been cloned and understanding their normal function and possible role in heart disease should be realized shortly.

III. BENEFITS OF BIOMEDICAL RESEARCH TO THE NATION AND THE STATE OF OREGON

A major challenge in health science in the next 10 to 20 years will be to translate the dramatic advances in biomedical research into new methods of prevention and cure of diseases. This will require close collaboration between basic scientists, biotechnologists and clinicians. Barriers between fields of research have to be broken down to encourage interdisciplinary approaches to science. A new biomedical research institute at the Oregon Health Sciences University in Portland is being developed for the purpose of fostering the kind of interdisciplinary approaches to science necessary to achieve this goal. Dr. Leonard Laster conceived this institute and Senator Hatfield has been instrumental in making it a reality. As the first director of the Institute of Advanced Biomedical Research, I would like to create an environment in which molecular biologists, neurobiologists, endocrinologists, cancer researchers and clinicians can interact with one another in a meaningful way to develop new approaches to research. The research focus of the institute will be the application of molecular biology to the study of the nervous system, behavior and disorders of the nervous system.

The new institute will increase visibility of the Health Sciences University in biomedical research and make the State of Oregon a more desireable place for biotechnology firms to locate. We expect the institute to be highly competitive in the quest for research support from public and private agencies and to attract some of the venture capital that is now flowing into the biomedical research field in abundance.

The development of the institute is not the only sign of a rebirth of science in the State of Oregon. New research centers are being developed at the Shriner's Hospital, VA Hospital, Beaverton Primate Center, and Good Samaritan Hospital. The overall impact of these developments on the public health and economy of the State of Oregon and the nation is likely to be considerable in the next 5 to 10 years. Perhaps as important is the fact that Oregonians will be able to participate in the revolution taking place in the health sciences.

Biography of Dr. Edward Herbert

DATE OF BIRTH: January 28, 1926

PLACE OF BIRTH: Hartford, Connecticut, USA

EDUCATION:

University of Connecticut, Storrs, Connecticut, B.S., 1949

University of Pennsylvania, Philadelphia, Pennsylvania, Ph.D., 1953

HONORS:

B.S. with high distinction, University of Connecticut

Harrison Fellowship, University of Pennsylvania, 1948-49

PHS Predoctoral Fellowship, University of Pennsylvania, 1950-53

PHS Postdoctoral Fellowship, University of Wisconsin, 1953-55

Career Development Award, University of Oregon, 1964-74

RESEARCH AND/OR PROFESSIONAL EXPERIENCE:

Instructor in Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, 1955-57

Assistant Professor of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, 1957-61

Associate Professor in Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts, 1961-63

Associate Professor of Chemistry, University of Oregon, 1963-66

Professor of Chemistry, University of Oregon, 1966-present

Visiting Professor, Neurobiology Department, Harvard University, 1971-72

Director, Institute of Advanced Biomedical Research, Oregon Health Sciences University, 1983 - present

Publications (not including abstracts)

E. Herbert, Phosphorylation of Nucleotides to Di- and Triphosphate Derivatives, Fed. Proc., 13, 276 (1954).

E. Herbert, Solitary Thyrotropin Deficiency with Secondary Hypothyroidism, Am. J. Med., XVII, 871 (1954).

E. Herbert, Phosphorylation of Pyrimidine Deoxyribosemononucleotides. Biochem. Biophys. Acta, 15, 134 (1954).

E. Herbert, Nucleotide Metabolism I. Phosphorylation of 5' - Uracil Nucleotides, J. Biol. Chem., 213, 923 (1955).

E. Herbert, Nucleotide Metabolism VI. Phosphorylation of 5' - Cytosine and Guanine Nucleotides, J. Biol. Chem., 222, 953 (1956).

E. Herbert, Liberation of Orthophosphate from ATP by Stromata of Human Erythrocytes, J. Cellular and Comp. Physiology, 47, 11-38 (1956). (Thesis)

E. Herbert, Incorporation of Pyrimidine Precursors into RNA in Cell-Free Fractions, Biochim. Biophys. Acta, 20, 439 (1956).

E. Herbert, V.R. Potter and H. I. Hecht, Incorporation of Orotic Acid into RNA of Cell-Free Fractions from Li er, J. Biol. Chem., 225, 659 (1957).

E. Herbert, Incorporation of Adenine Nucleotides into Ribonucleic Acid by Enzymes Purified from Rat Liver, Fed. Proc. 17, 950 (1958).

E. Herbert, The Incorporation of Adenine Nucleotides into RNA by Cell-Free Systems, J. Biol. Chem., 231, 975 (1958).

E. Herbert, Reactions of Terminal Groups of RNA in Animal Systems, Ann. N.Y. Acad. Sci., 81, 679 (1959).

E. Herbert and E.S. Canellakis, Studies on Soluble RNA Synthesis I. Purification and General Properties of the RNA-Enzyme Complex, Proc. Nat. Acad. Sci., (USA) 46, 170 (1960).

E. Herbert and E.S. Canellakis, Studies on Soluble RNA Synthesis II. Purification Procedure, Biochim. Biophys. Acta, 42, 133 (1960).

E. Herbert, Studies on Soluble RNA Synthesis III. Analytical Studies on sRNA of Rat Liver, Biochim, Biophys. Acta, 42, 363 (1960).

E. Herbert and E.S. Canellakis, Studies on Soluble RNA Synthesis IV. The Effect of Inorganic Pyrophosphate and a Method for the Extraction of sRNA, Biochim. Biophys. Acta, 47, 78 (1961).

E. Herbert and E.S.. Canellakis, Studies on Soluble RNA Synthesis V. Reconstitution of a Biological Property of Phosphodiesterase-Treated sRNA, Biochim. Biophys. Acta 47, 85 (1961).

E. Herbert and E.S. Canellakis, Enzymatic Synthesis of Defined Nucleotide Sequences in sRNA, in Symposium on Biological Structure and Function, First IUBS Congress, Stockholm, Sweden (1960).

E. Herbert, Purification of Enzymes that Incorporate Ribonucleotides into sRNA, in Methods in Enzymology, Vol. VI, Academic Press, New York, (1960).

E. Herbert, Characteristics of sRNA-Enzyme Complexes Isolated from Liver, Fed. Proc. 19: 318 (1960).

E. Herbert and C.W. Wilson, Determination of Nucleotide Sequences in Soluble Ribonucleic Acid. I. Pyrophosphorolysis and Reconstitution of a Fraction of Soluble Ribonucleic Acid, Biochim. Biophys. Acta, 61, 750 (1962).

E. Herbert and C.W. Wilson, Determination of Nucleotide Sequences in Soluble Ribonucleic Acid. II. Determination of Nucleotide Sequences in Oligonucleotides Derived from the Acceptor End of Pyrophosphorolyzed Soluble Ribonucleic Acid, Biochim. Biophys. Acta, 61, 762 (1962).

E. Herbert and C.J. Smith, Valine Oligonucleotide Complexes Produced by T_1 Ribonuclease from Valine Acceptor RNA, Biochim. Biophys. Acta, 87, 341 (1964).

E. Herbert, C.J. Smith and C.W. Wilson, Isolation of Oligonucleotides from the Acceptor End of Amino Acid Specific Acceptor Chains of Soluble RNA, J. Mol. Biol., 9, 376 (1964).

E. Herbert and W. Godchaux, Effect of Chloramphenicol on Protein Synthesis, ATP Content, and Polyribosomes in Intact Reticulocytes, Fed. Proc., 24 1976 (1965).

E. Herbert, C.E. Holt and P. Joel, Turnover of Terminal Nucleotides of Soluble RNA in Intact Reticulocytes, J. Biol. Chem, 241 1819 (1966).

E. Herbert, C.J. Smith and P. Smith, Isolation of Amino Acyl-Oligonucleotides from T_1 Ribonuclease Digests of sRNA Charged with Serine, Glycine, Threonine, and Alanine, Biochemistry, 5 , 1323 (1966).

E. Herbert and C.J. Smith, Structure of Amino Acyl-Oligonucleotides Derived from T_1 Ribonuclease Digests of sRNA Charged with Serine, Alanine, Glycine, Threonine, Biochemistry, 5, 1333 (1966).

W. Godchaux, III and E. Herbert, The Effect of Chloramphenicol in Intact Erythroid Cells, J. Mol. Biol., 21, 537 (1966).

Godchaux, III, S. Adamson and E . Herbert, Effects of Cycloheximide on Polyribosome Function in Reticulocytes, J. Mol. Biol, 27, 57 (1967).

E. Herbert and C.J. Smith, Ribonuclease Sensitivity of GMP Sites in Yeast Acceptor RNA Charged with Tyrosine, Alanine, Phenylalanine and Glycine, J. Mol. Biol. 28, 281 (1967).

Herbert, E. and E.S. Canellakis. Purification and Assay of Enzyme-RNA Complexes from Rat Liver. Vol. VI, Methods in Enzymology, Academic Press (1967).

Herbert, E. and C.J. Smith. Structure of Aminoacyl-Oligonucleotides Derived from T_1 Ribonuclease Digests of sRNA Charged with Tryrosine and Phenylalanine. Biochemisty 7 (1967).

Godchaux, W.G., S.D. Adamson and E. Herbert. Regulations of the Rate of Protein Synthesis in Reticulocytes. Archives of Biochim. and Biophys. 125: 671 (1968).

Wong, J. and E. Herbert. Regulation of Amino Acid Specific sRNA synthesis in E. coli Biochim. Biophys. Acta. 174: 513 (1969).

Herbert, E., S.D. Adamson and S.K. Kemp. Effects of Hemin and other Porphyrins on Protein Synthesis in a Reticulocyte Lysate Cell-Free System. J. Mol. Biol. 42: 247 (1969).

Herbert, E., S.D. Adamson and G.A. Howard. The Ribosome Cycle in a Reconstituted Cell-Free System from Reticulocytes. Cold Spring Harbor Symp. Quant. Biol. 34: 547 (1969).

Herbert, E., G. Howard and S.D. Adamson. Cessation of Protein Synthesis in Cell-Free Systems from Reticulocytes. Biochim. Biophys. Acta, 213: 237 (1970).

Herbert, E., G.A. Howard and S.D. Adamson. Subunit Recycling during Translation in a Reticulocyte Cell-Free System. J. Biol. Chem. 245: 6237 (1970).

Herbert, E. and R.W. Morris. Purification and Characterization of Yeast Nucleotidyl Transferase and Investigation of Enzyme-Transfer Ribonucleic Acid Complex Formation. Biochemistry 9: 4819 (1970).

Herbert, E. and R.W. Morris. Stoichiometry of Yeast Nucleotidyl Transferase and Effect on the Addition Reaction of Stepwise Removal of Nucleotides from the Acceptor End of the Transfer Ribonucleic Acid. Biochemistry 9: 4828 (1970).

Adamson, S.D., P. Yau, E. Herbert and W.V. Zucker. Involvement of Hemin; A stimulatory fraction from ribosomes and a protein synthesis inhibitor in the regulation of hemoglobin synthesis. J. Mol. Biol. 62: 247 (1971).

Hildebrand, J.G., D.L. Barker, E. Herbert and E.A. Kravitz. Screening for neurotransmitters: a rapid radiochemical procedure. J. Neurobiol. 2: 231 (1971).

Barker, D.L., E. Herbert, J.G. Hildebrand and E.A. Kravitz. Acetylcholine and lobster sensory neurons. J. Physiol. (London) 226: 205 (1972).

Woodward, W.R. and E. Herbert. Efficiency of codon recognition by lysine isoacceptor tRNAs in hemoglobin synthesis. Science 177: 1197 (1972).

Woodward, W.R., S.D. Adamson, H.M. McQueen, J.W. Larson, S.M. Estvanik and E. Herbert. Globin synthesis on reticulocyte membrane bound ribosomes, J. Biol. Chem. 248: 1556 (1973).

Woodward, W.R., J.L. Ivey and E. Herbert. Protein synthesis with rabbit reticulocyte preparations. Methods in Enzymology 30: 724-731 (1973).

Woodward, W.R. and E. Herbert. Preparation and characterization of an inhibitor of globin synthesis from the postribosomal supernatant of reticulocyte lysates. Methods in Enzymology 30: 731-740 (1973).

Woodward, W.R., P. Wilairat and E. Herbert. Preparation of retriculocyte aminoacyl-tRNA and the assay of codon recognition properties in isoacceptor tRNAs in a reticulocyte cell-free system. Methods in Enzymology 30: 740-746 (1973).

Woodward, W.R. and E. Herbert. Preparation and analysis of nascent chains on reticulocyte membrane-bound ribosomes. Methods in Enzymology 30: 746-748 (1973).

Eipper, B.A. and R.E Mains. On the existence of high molecular weight forms of ACTH, Biochemistry 14: 3836 (1975).

Mains, R.E. and B.A. Eipper. Subunit molecular weights of ACTH in extracts of the anterior and intermediate - posterior lobes of mouse pituitary. Proc. Natl. Acad. Sci. USA 72: 3656 (1975).

Howard, G.A. and E. Herbert. Ribosomal subunit localization of hemoglobin messenger RNA. Eur. J. Biochem. 54: 75 (1975).

Wilairat, P. W.R. Woodward and E. Herbert. Precision of Initiation of globin synthesis in a rabbit reticulocyte cell-free system. J. Sci. Thailand 1: 188 (1976).

Mains, R.E. and B.A. Eipper. Biosynthesis of adrenocorticotropic hormone in mouse pituitary tumor cells. J. Biol. Chem. 251: 4115 (1976).

Eipper, B.A., R.E. Mains and D. Guenzi. High molecular weight forms of adrenocorticotopic hormone are glycoproteins. J. Biol. Chem. 251: 4121 (1976).

Johnson, A.E., W. R. Woodward, E. Herbert and J.R. Menninger. N -acetyllysine transfer ribonucleic acid; a biologically active analogue of aminoacyl transfer ribonucleic acids. Biochemistry 15: 569 (1976).

Eipper, B.A. and R.E. Mains. Peptide analysis of a glycoprotein form of adrenocorticotropic hormone. J. Biol. Chem. 252: 8821 (1977).

Roberts, J.L. and E. Herbert. Characterization of a common precursor to corticotropin and β-lipotropin: cell-free synthesis of the precursor and identification of corticotropin peptides in the molecule. Proc. Natl. Acad. Sci. USA 74: 4826 (1977a).

Roberts, J.L. and E. Herbert. Characterization of a common precursor to corticotropin and β-lipotropin: identification of β-lipotropin peptides and their arrangement relative to corticotropin in the precursor synthesized in a cell-free system. Proc. Natl. Acad. Sci. USA 74: 5300 (1977b).

Herbert, E., R.G. Allen and T.L. Paquette. Reversal of dexamethasone inhibition of adrenocorticotropin release in a mouse pituitary tumor cell line either by growing cells in the absence of dexamethasone or by addition of hypothalamic extract. Endocrinology 102: 218 (1978).

Roberts, J.L., M. Phillips, P.A. Rosa, and E. Herbert, Steps involved in the processing of common precursor forms of adrenocorticotropin and endorphin in cultures of mouse pituitary cells, Biochemistry 17, 3609 (1978).

Allen, R.G., E. Herbert, M. Hinman, H. Shibuya and C.B. Pert, Coordinate control of corticotropin, β-lipotropin, and β-endorphin release in mouse pituitary cell culture, Proc. Natl. Acad. Sci. USA, 75, 4972 (1978).

Herbert, E., J.L. Roberts, M. Phillips, P.A. Rosa, M. Budarf, R.G. Allen, P.F. Policastro, T.L. Paquette, and M. Hinman, Biosynthesis and processing of a common precursor to adrenocorticotropin and β-lipotropin in mouse pituitary cells, in Symposium on Endorphins in Mental Health Research, MacMillan Press, (1979).

Roberts, J.L. M. Phillips, P.A. Rosa, M. Budarf, and E. Herbert, Processing of common precursor forms of adrenocorticotropin and endorphins in cultures of mouse pituitary cells and in mouse pituitary, in ICN Symposium, J. of Supramolecular Structure, Vol. 2, (1979).

Roberts, J.L., M. Budarf, R.G. Allen, J.D. Baxter, and E. Herbert, Effect of glucocorticoids on the synthesis and processing of the common precursor to adrenocorticotropin and endorphin in mouse pituitary tumor cells, in Volume 6 of Conference on Cell Proliferation, Cold Spring Harbor Laboratory, New York (1978).

Herbert, E., J.L. Roberts, M. Hinman, M. Phillips, and M. Budarf, Biosynthesis of the common precursor to ACTH and endorphin in pituitary cell culture systems, Biochemical Endocrinology: Synthesis and Release of Adenohypophyseal Hormones, Cellular and Molecular Mechanisms, Plenum Press, (1979).

J.L. Roberts, P.H. Seeburg, J. Shine, E. Herbert, J.D. Baxter, and H.M. Goodman Corticotropin and β-endorphin: construction and analysis of recombinant DNA complementary to mRNA for the common precursor, Proc. Natl. Acad. Sci. USA 76, 2153 (1979).

Thomas L. Paquette, E. Herbert, and M. Hinman, Molecular weight forms of adrenocorticotropic hormone secreted by primary cultures of mouse anterior pituitary, Endocrinology 104, 1211 (1979).

E. Herbert, J.L. Roberts, M. Phillips, R. Allen, M. Hinman, M. Budarf, P. Policastro, and P. Rosa, Biosynthesis, processing and release of corticotropin, β-endorphin, and melanocyte stimulating hormone in pituitary cell culture systems, Chapter in Frontiers in Neuroendocrinology 6, ed. by W.F. Ganong and L. Martini, Raven Press, New York 67-100 (1980).

E. Herbert, M. Budarf, M. Phillips, P. Rosa, P. Policastro, and E. Oates, Presence of a pre-sequence in the common precursor to ACTH and endorphin and the role of glycosylation in processing of the precursor and secretion of ACTH and endorphin, in Annals of the New York Academy of Sciences 79-93 (1979).

J.L. Roberts, M.L. Budarf, J.D. Baxter, and E. Herbert, Selective reduction of pro-ACTH-endorphin proteins and messenger RNA activity in mouse pituitary tumor cells by glucocorticoids, Biochemistry 18, 4907 (1979).

Allen, Richard, Orwoll, G.E., Kendall, John, Herbert, Edward, and Paxton, Harold, The distribution of forms of ACTH and β-endorphin in normal, tumor and autospy human anterior pituitary tissue; absence of 13K ACTH. Journal of Clinical Endocrinology and Metabolism 51, 376-380 (1980).

Hinman, Michael and Herbert, Edward, Processing of the Precursor to Adrenocorticotrophic Hormone and β-lipotropin in Monolayer Cultures of Mouse Anterior Pituitary, Biochemistry 19, 5395-5402 (1980).

Herbert, E., Processing of Cellular and Viral Polyproteins, Nature 288, 45 (1980).

Rosa, PA., Policastro, P., and Herbert, E., A Cellular Basis for the Differences in Regulation of Synthesis and Secretion of ACTH/Endorphin Peptides in Anterior and Intermediate Lobes of the Pituitary. J. Experimental Biology (England) 89, 215-237 (1980).

Phillips, M., Budarf, M., and Herbert, E., Glycosylation Events in the Processing and Secretion of pro-ACTH-endorphin in Mouse Pituitary Tumor Cells, Biochemistry, 20, 1666-1675 (1981).

Policastro, Paul, Phillips, Marjorie, Oates, Edward, Herbert, Edward, Roberts, J.L., Seidah, N., and Chretien, M., Evidence for a Signal Sequence at the N-terminus of the common precursor to adrenocorticotropin and β-lipotropin in Mouse Pituitary Cells, Eur. J. Biochem. 116, 255-259 (1981).

Herbert, E., Expression of Cellular Polyproteins, Trends in Biochemical Science 184 (1981).

Herbert, E., Phillips, M. and Budarf, M., Glycosylation Steps Involved in Processing of Pro-Corticotropin-Endorphin in Mouse Pituitary Tumor Cells, Methods in Cell Biology 23, Academic Press, (1981).

Herbert, E., Birnberg, N., Civelli, O., Lissitzky, J.C. and Uhler, M., Pro-opiomelanocortin: A Model for the Regulation of Expression of Neuropeptides in Pituitary and Brain, Neuroscience Newsletter 12:5, 16-27 (1981).

Comb,M. and Herbert, E., Partial Characterization of the mRNA that codes for Enkephalins in Bovine Adrenal Medulla and Human Pheochromocytoma, Proc. Natl. Acad. Sci. USA 79, 360-364 (1982).

Comb, M., Seeburg, P., Adelman, J., Eiden, L. and Herbert, E., Primary Structure of the Human Met- and Leu-enkephalin Precursor and its mRNA, Nature 295, 663-666 (1982).

Civelli, O., Birnberg, N., and Herbert, E., Detection and Quantitation of Pro-opiomelanocortin mRNA in Pituitary and Brain Tissues from Different Species, J. Biological Chemistry 257, 6783-6787 (1982).

Herbert, E., and Uhler, M., Biosynthesis of Polyprotein Precursors to Regulatory Peptides, Cell 30, 1-2 (1982).

Roberts, J.L., Chen, C., Eberwine, J.H., Evinger, M., Gee, C., Herbert, E. and Schachter, B.S., Glucocorticoid regulation of pro-opiomelanocortin gene expression in rodent pituitary, Recent Progress in Hormone Research 38: 227-256 (1982).

Allen, R.G., Hinman, M. and Herbert, E., Forms of corticotropin and β-endorphin released by partially purified CFR in mouse anterior pituitary cultures. J. of Neuropeptides 2: 175-184 (1982).

Budarf, Marcia L. and Herbert, E., Effect of Tunicamycin on the Synthesis, Processing, and Secretion of Pro-opiomelanocortin Peptides in Mouse Pituitary Cells, Journal of Biological Chemistry, 257, 10128-10135 (1982).

Herbert, E., Birnberg, N., Civelli, O., Lissitzky, J.C., Uhler, M., and Durrin, L., Regulation of Genetic Expression of Pro-Opiomelanocortin in Pituitary and Extrapituitary Tissues of Mouse and Rat, Regulatory Peptides, from Molecular Biology to Function, Raven Press (1982).

Herbert, E., Birnberg, N. Lissitzky, J.C., Civelli, O., Uhler, M., Regulation of Expression of Pro-Opiomelanocortin and Related Genes in Various Tissues of the Rat and Mouse, Serono Symposium No. 49, "Pituitary Hormones and Related Peptides" Academic Press (1982).

Herbert, E., Civelli, O., Birnberg, N. Rosa, P. and Uhler, M., Regulation of Expression of Pro-Opiomelanocortin and Related Genes in Various Tissues: Use of Cell-Free Systems and Hybridization Probes, Molecular Genetic and Neuroscience, 219-230, Raven Press (1982).

Uhler, M. and E. Herbert. Complete Amino Acid Sequence of Mouse Pro-opiomelanocortin Derived from the Nucleotide Sequence of Pro-opiomelanocortin cDNA. J. Biol. Chem. 258: 257-261 (1983).

Uhler, M., Herbert, E., D'Eustachio, P., and F. Ruddle (1983) The mouse genome contains two nonallelic pro-opiomelanocortin genes, J. Biol. Chem. 258:9444-9453.

Comb, M., Rosen, H., Seeburg, P., Adelman, J., and E. Herbert (1983) Primary structure of the human proenkephalin gene, DNA 2:213-229.

Birnberg, N., Lissitzky, J-C., Hinman, M. and E. Herbert (1983) Glucocorticoids regulate proopiomelanocortin gene expression in vivo at the levels of transcription and secretion, Proc. Natl. Acad. Sci. USA 80: 6982-6986.

Civelli, O., Birnberg, N., Comb, M., Douglass, J., Lissitzky, J-C, Uhler, M., and E. Herbert (1983) Regulation of opioid gene expression, Peptides 4: 651-656.

Herbert, E., Oates, E., Martens, G., Comb, M., Rosen, H., and M. Uhler (1983) Generation of diversity and evolution of opioid peptides. Cold Spring Harbor Symposia on Quantitative Biology, Vol. 48, Molecular Neurobiology, Cold Spring Harbor Laboratory, New York, pp. 375-384.

Civelli, O., Oates, E., Rosen, H., Martens, G., Comb, M., Douglass, J. and E. Herbert (1983) Expression of the Opioid Genes, In: Biochemical and Clinical Aspects of Neuropeptides: Synthesis, Processing and Gene Structure (Eds. Kock, G. and Richter, D.) Academic Press, New York, pp. 45-57.

Herbert, E., Comb, M., Rosen, H., and G. Martens (1984) Expression of opioid peptide genes in different species, In: Cellular and Molecular Biology of Neuronal Development (Ed. I.B. Black), Plenum Press, New York, pp. 279-307.

Douglass, J., Civelli, O. and E. Herbert (1984) Polyprotein Gene Expression: Generation of Diversity of Neuroendocrine Peptides. In: Annual Review of Biochemistry, vol. 53, pp. 665-715.

Martens, G.J.M. and E. Herbert (1984) Polymorphism and absence of leu-enkephalin sequences in Xenopus laevis, Nature 310: 251-254.

Oates, E. and E. Herbert (1984) 5' Sequence of porcine and rat pro-opiomelanocortin mRNA: One porcine and two rat forms, J. Biol. Chem. 259: 7421-7425.

Eiden, L., Giraud, P., Affolter, H-U., Herbert, E., and A. Hotchkiss (1984) Alternative modes of enkephalin biosynthesis regulation by reserpine and cyclic AMP in cultured chromaffin cells, Proc. Natl. Acad. Sci. USA. 81: 3949-3953.

Papers in Press

Herbert, E., Uhler, M. and M. Comb (1984) Biosynthesis of Polypeptide Hormones, In: The Endocrine Lung in Health and Disease, (K.L. Bicker and A. Gazdar, eds), W.B. Saunders Company, Philadelphia (in press).

Douglass, J., Civelli, O., Birnberg, N., Comb, M., Uhler, M., Lissitzky, J-C., and E. Herbert (1984) Regulation of expression of opioid peptide genes, Annals of Neurology (in press).

Herbert, E., Civelli, O. and J. Douglass (1984) Generation of Diversity of Opioid Peptides, In: Biochemical Actions of Hormones, vol. 12, Academic Press (in press).

Civelli, O., Douglass, J. and E. Herbert (1984) POMC, A Polyprotein at the Interface of the Endocrine and Nervous Systems, In: The Peptides, vol. 7, (in press).

Rosen, H.,Douglass, J. and E. Herbert (1984) Isolation and characterization of the Rat Proenkephalin Gene, J. Biol. Chem. (in press)

Abstracts

In addition to the above, 65 Abstracts have been submitted to various meetings for presentation of papers or posters in the past 20 years. I have most of the titles available, if they are of interest.

Presentation of Papers at National and International Meetings in Past Five Years

1978

Conference on Endorphins in Mental Health, San Juan, Puerto Rico, December 1977.

UCLA-ICN Conference, Keystone, Colorado (on polypeptide hormones), February 1978.

International Congress of Biochemical Endocrinology in Blois, France, September 1978.

Symposium on Hormones and Cell Culture at Cold Spring Harbor, Long Island, New York, August 1978.

Montreal Cancer Research Institute (Received Pfizer Award for Neuroendocrinology given by Clinical Research Institute of Montreal. A traveling fellowship gave two lectures at the Institute.)

1979

Gordon Research Conference lecture, February 2, 1979, Santa Barbara (on Hormone Action).

New York Academy of Sciences Meeting on Protein Processing, May 3-5, 1979.

Gordon Research Conference Talk (Biological Regulation), June 25-28, 1979 - New Hampshire.

Gave one of 3 plenary lectures at Symposium on Neurotransmission, Woods Hole, Mass., July 2-4, 1979.

Speaker at Symposium on Cell-Secretion, Sponsored by NIH, Annapolis, Maryland, September 16-20, 1979.

Weizmann Institute of Science, Rehovoth, Israel -- Gave series of lectures at invitation of Biochemistry and Hormone Research Groups (Yigal Burstein), November 29 - December 15, 1979.

1980

Gordon Conference on Hormones - February.

American Society of Biological Chemists Symposium Talk - April

Symposium talk at Conference on Protein Processing, Hamburg, Germany, May 25-28

Gordon Research Conference on Opiate Peptides, June 25-28

2 lectures in Course on Neurobiology at Cold Spring Harbor, Long Island - July 2-5

2 lectures in course on neurobiology at Woods Hole Marine Biology Laboratory

Plenary lecture at International Society of Biochemical Endocrinology Meeting in Dubrovnik, Yugoslavia - September 25

Chaired and organized Symposium on Neuropeptide Biochemistry at Neurosciences Meeting in Cincinnati, Ohio - November 9-12. Also gave a symposium talk.

1981

3rd Annual Cellular and Molecular Endocrinology Symposium at Riverside, California - April 2-4.

Workshop on Molecular Biology and Neuroscience, Woods Hole, Mass. - May 2-9.

Plenary Lecture at International Symposium on Neuropeptides, San Marino, Italy - May 25-28.

Gordon Conferences on Biological Regulation and on Molecular Pharmacology - June 25.

Teaching in the Neurobiology Course at Cold Spring Harbor, LI - July 5-8.

Symposium on Polypeptide Hormones (International Society of Endocrinology and Pharmacology) Kyoto, Japan - July 26-30.

Symposium on Regulation of Gene Expression (Neuroactive Peptides), Italy - August 28 - September 2.

Symposium on Application of Molecular Genetics to the Nervous System, Neuroscience Meeting in Los Angeles, November 10-18.

1982

Gordon Research Conference on Biological Regulation, Holderness, New Hampshire, June 21-25. Chaired session on Bioactive Peptides.

Symposium on Neuropeptides at University of North Carolina, March 3-5.

Oregon Molecular Biology Meeting, May 5. Symposium talk.

Course on Synapse and Sensory Transduction, July 22-25, Cold Spring Harbor - two lectures.

3rd Annual Leslie Bennett Lecture, July 7, San Francisco, University California at San Francisco.

Symposium on Endocrine Lung in Health and Disease, June 2-4, Washington, D.C.

Symposium on Molecular Approaches to the Nervous System, August 9-15, Cold Spring Harbor, Long Island

Inserm Symposium on Polypeptide Gene Expression, October 3-7, Blois, France

Plenary lecture at Symposium on Bioactive Peptides in the Nervous System, November 9-10, University of Michigan

Workshop on Etiology of Epilepsy, December 3-7, Kroc Froundation, Santa Ynez, California

1983

Symposium on Cellular and Molecular Biology of Neuronal Development, St. Thomas, March 2 - 5

Seminar to St. Jude Children's Research Hospital faculty and trainees, Memphis, Tennessee, March 18

Symposium on Enkephalins: Synthesis, Metabolosm and Function, American Society for Neurochemistry, 14th annual meeting, Honolulu, March 21 - 25

Conference on Biochemical and Clinical Aspects of Neuropeptides: Synthesis, Processing and Gene Structure, Hamburg, Germany, May 29 - June 2

Aldosterone Conference, San Antonio, Texas, sponsored by The University of Oklahoma Health Sciences Center, June 6-7

Course on Molecular and Cellular Neurobiology, July 13-16, Cold Spring Harbor

Gordon Conference on Neuroplasticity, July 18-22, Wolfboro, New Hampshire

Ferring Symposium on Biogenetics of Neurohormonal Peptides, Stockholm
July 1-2

Gordon Conference on Developmental Biology, Chairman, July 25-29

Gordon Conference on Catecholamines, August 1-5

Keynote Speaker, 33rd Annual Symposium on the Biology of Skin, Cutaneous Oncogenic Viruses, Salishan Lodge, Oregon, October 9-13

International Symposium on Basic Mechanisms of the Epilepsies, San Diego
December 7-10

22nd Annual Meeting of American College of Neuropsycholopharmacology,
San Juan, Puerto Rice, December 12-16

Honors in Past Four Years

(1) Pfizer award in 1978 for Fundamental Contributions to Endocrinology, Clinical Research Institute of Montreal and McGill University

(2) Rosetta Briegal Award in 1981 by University of Oklahoma for Pioneering work in Biochemistry

(3) Leslie Bennett Award in Endocrinology in 1982 by University of California San Francisco

(4) McKnight Foundation Distinguished Research Award for pioneering research in 1982 and 1983, awarded in March 1984.

(5) Lamport Lecture Award, University of Washington, Seattle, awarded May, 1984

Dr. HERBERT. Thank you, Senator Hatfield and Senator Domenici. I appreciate the opportunity to comment on the importance of biomedical research at this time. I believe that this is the most exciting period in biology that I've experienced since I've been in the field.

The reason is that dramatic discoveries in biology, particularly in molecular biology and genetics, are reshaping our thinking about how to practice medicine and how to deliver health care. I think a major challenge in the next 10 to 15 years is how to translate these dramatic advances into specific prevention measures and cures, and I would like to talk about that a little bit later.

In the few minutes that I have before you, I would like to describe the impact of some of these discoveries on the future course of the health sciences and on the practice of medicine.

Now molecular biology and genetics have provided us with some very powerful new tools for studying human biology. One of the first tools is the capacity to separate all of the genes in the human cell, of which there are more than 2 million, and to analyze the function of each of these genes. Now this is a critical thing because genes control all of the activities of cells and behavior of organisms.

Second, it is now possible to take these genes—what we call clone genes—and transfer them from one cell to another or from one organism to another and to change the genetic makeup of the organism. It has been possible, for example, to produce giant mice by transferring a rat growth hormone into a mouse embryo. This ability is going to alter

our way of doing genetics in the future and will make it possible, I think, for us to correct specific genetic defects in the future in human beings. And I just wanted to point out that yesterday I received a copy of Chemical and Engineering News which contains a complete description of some of the ways in which molecular biology is going to affect the study of human genetics, and they describe some of the ways in which the organisms' makeup can be changed and some of the problems involved. A very important piece of information, I think.

Now one of the ways in which these tools have been used to study specific diseases is how molecular biology has been used to study cancer. We have been able to—and when I say "we", I mean the scientific community—have been able to isolate specific genes called oncogenes that control the transformation of normal cells into cancer cells. Upon a signal from a virus or a chemical, these genes become active and promote the growth of the cell and the invasion of normal tissues; and I think that Dr. Kabat will talk to you a little bit more about that.

But what this opens up is the possibility for identifying the specific products of those genes and intervening in their actions in cancer cells. So we hope that in the near future this will lead to some specific preventative measures for some specific kinds of cancer.

Second, molecular biology has enabled us to isolate specific genes that are defective in certain degenerative diseases, such as Huntington's chorea, a 100-percent fatal syndrome in human beings.

Third, an area that I am most interested in myself is that molecular biology has led to dramatic advances in our understanding of brain chemistry, behavior, and dysfunctions of behavior in the last 5 to 10 years. We have discovered that the brain contains many kinds of chemicals that we didn't know about before that control specific behavior patterns, such as sleep, sexual cycles, learning, memory, pain, stress, and so on.

Now these chemicals, called neuropeptides, are produced in specific pathways in the nervous system where they mediate these responses. An important practical implication is that many drugs that we ingest, such as morphine or valium, act on behavior—that is, altered behavior—by mimicking the actions of the body's own neuropeptides.

For example, the body produces substances that regulate our perception of pain, such as endorphins and enkephalins—you may have heard of them—neuropeptides that control pain and act very much like morphine. The concept has arisen, because of these findings, that every drug that we take in is mimicking the action of some natural component that we normally produce ourselves. Now if we can understand how these normal components are produced and what they are, we can use them as therapy for mental disorders, and to modify behavior in a much more specific way than is now possible. And many drug companies are now interested in these possibilities. These discoveries are really reshaping our thinking about the design of therapeutic agents and how we might modify behavior.

The discovery of these new chemicals has also led to some new concepts about some of man's most sophisticated activities, such as learning and memory. We now know of specific neuropeptides that modulate our ability to think, to recall, and to learn. So we are in a position through the benefits of molecular biology to, I think, learn a great deal about how the brain functions in the next 10 years, and about some of the dysfunctions of the brain.

Finally, I would like to turn to what, I think, are some of the benefits of these discoveries to the Nation and the State of Oregon. I think a major challenge in the health sciences in the next 10 to 20 years will be to translate some of the discoveries that I've spoken of into new methods for prevention and cure of diseases.

I think one of the most important aspects of accomplishing this will be the close collaboration between basic scientists, biotechnologists, clinicians, and other people who are delivering health care. Now what we have to do is to break down the barriers between fields of research and between these groups of people to encourage interdisciplinary approaches to science, and translating these benefits into treatment and cures.

The new Biomedical Research Institute at the Oregon Health Science University in Portland, which Dr. Laster has spoken of, is being developed for the purpose of fostering this kind of interdisciplinary approach. And this is necessary to achieve this goal. Now Dr. Laster conceived this institute and Senator Hatfield has been instrumental in making it a reality.

As the first director of this institute, I would like to create an environment in which molecular biologists, neurobiologists, endocrinologists, and clinicians can interact with one another in a meaningful way to produce new approaches to research. And I would like to focus the research in the institute on the application of molecular biology and modern approaches to genetics to the study of the nervous system and to disorders of the nervous system.

I think the new institute and other developments in the State of Oregon will increase the visibility of the health sciences in the State of Oregon as a place for biotechnology firms to locate. I would also expect that the institute would be highly competitive in the quest for research funds from both public and private agencies. And I am particularly hopeful that we will attract some of the venture capital that is now flowing into biomedical research in great abundance in other parts of the country. I hope we can attract some of that to this part of the country.

The development of the institute is not the only sign of rebirth of science in the State of Oregon. New research centers are being developed at the Shriner's Hospital, the Veterans' Hospital, Beaverton Primate Center, existing research centers—molecular biology at the University of Oregon—very high quality—and Oregon State University are also another important resource for us.

The overall impact of these developments on the public health and economy of the State of Oregon and the Nation is likely to be considerable in the next 5 to 10 years. But perhaps as important as this is the fact that these developments will allow Oregonians—not just you and I but other Oregonians—to participate actively in the revolution that's taking place in the health sciences. Thank you very much.

Senator HATFIELD. Thank you, Dr. Herbert.

Senator DOMENICI. Thank you very much, Doctor.

Senator HATFIELD. Thank you again, Dr. Herbert, for your fine testimony.

STATEMENTS OF:

DR. DAVID KABAT, PROFESSOR OF BIOCHEMISTRY, OREGON HEALTH SCIENCES UNIVERSITY

DR. EDWARD NEUWELT, ASSOCIATE PROFESSOR OF NEUROSURGERY, ASSISTANT PROFESSOR OF BIOCHEMISTRY, OREGON HEALTH SCIENCES UNIVERSITY

PREPARED STATEMENT

Senator HATFIELD. I would like to invite now both Dr. David Kabat, professor of biochemistry, and Dr. Edward Neuwelt, associate professor of neurosurgery and assistant professor of biochemistry, to come to the table at this time; and, gentlemen, if you would like to submit your formal statement for the record and summarize it to some degree, we would appreciate that very much. We're very happy to have both Dr. Neuwelt and Dr. Kabat testifying here today. We're happy to see the youth of all of these people, too. We expect to have you around a long time.

[The statement follows:]

40-856 O - 85 -- 4

Statement of Dr. David Kabat

Background

I will give you a brief description of my background and of the biomedical research in which I am engaged. I am a Professor of Biochemistry in the School of Medicine at the Oregon Health Sciences University. I arrived here 15 years ago from the Massachusetts Institute of Technology to become an Assistant Professor, and I had previously received my Ph. D. degree from the California Institute of Technology. I have also worked for shorter periods at the Weizmann Institute in Israel and at the Netherlands Cancer Institute.

My field is cancer research done using molecular biology and recombinant DNA technology. My specific interest is in leukemia which is a cancer that affects blood cells. As you know, cancer cells grow out of control and in disarray. They grow in the wrong places and cancer tissue therefore looks disorganized and abnormal in its overall architecture. Recently, scientists have been able to take DNA from cancer cells and to introduce it into normal cells. Interestingly, this cancer DNA can transform the normal cells into cancer cells. Using this approach, cancer genes (called "oncogenes") have been discovered.

The next to last page of my written statement shows the structure of an oncogene which we discovered and sequenced using recombinant DNA techniques. When this leukemia gene is introduced into normal mouse bone marrow cells, they begin to proliferate wildly. Genes are linear polymers composed of four subunits so they are written in a two-dimensional language. However, genes code for proteins which have three-dimensional structures. The last page of my written statement shows a three-dimensional model of the leukemia-causing protein. The leukemia molecule has a dumbell shape with two globular regions held together by a flexible coil. The smaller globular region has a hook that causes the molecule to attach to cell membranes. These dumbell shaped molecules coat the outer surface membranes of the leukemia cells and they cause the cell to grow wildly and to cause death of the individual.

I've described this background to illustrate that I've worked in excellent institutions and that I am now in Oregon using modern recombinant DNA techniques to learn about cancer. My work may have practical benefit or it may just contribute to our knowledge concerning our place in the universe and the reasons why we have disease and suffering. I've also participated in the peer review system by which funds are granted.

Conclusions About Science and the Impact of Science Policy on Small Institutions and Small States Such as Oregon

Science is autocatalytic. It grows where there is existing science because that is where good students are trained, libraries are found, and technical advice can be obtained. Therefore, seed money tends to have an important positive impact. Consequently, a dollar spent on a good project in a less advanced region of the country has more impact than a dollar spent on a similar project in an already established research center. As far as I know, there is no provision in the peer review system which takes account of this seed benefit that can accompany grant funding.

Because science is autocatalytic, we have seen the growth of scientific research centers. Generally, these contain universities or federal laboratories surrounded by related industries. Although such centers are important for our scientific enterprise, they also create a situation where taxpayer dollars get funneled away from some regions and into other areas of the country.

The history of biomedical research in this country also supports the conclusion that scientific breakthroughs often occur in small institutions far removed from the major research centers. The origin of the California Institute of Technology provides one excellent example. Genetic research and the field of biochemical genetics was begun there by scientists who wanted to start a new field far from the dogmas that had dominated their science. Most

of Barbara McClintock's Nobel prize work on jumping genes of corn also was performed alone.

Although excellent and important, the peer review system works to favor the larger research centers. Often, peer review committees wonder whether relatively isolated scientists can work effectively. Availability of collaborators is viewed very favorably. Also, a substantial proportion of research funding has gone to program project and center grants which support large collaborative projects rather than research grants to individual investigators. Small institutions have little chance to obtain program project grants.

Economic Implications of Modern Biomedical Research

Science has become central to our health and to our economy, and much of our future industry will depend upon the scientific endeavor. Molecular biology is undoubtedly going to contribute to these developments. Already, for example, it is providing clinical laboratories with standardized uniform reagents for diagnostic purposes. The U.S. is now the leader in this field. The breakthroughs which led to recombinant DNA and monoclonal antibody technologies developed from individual basic science projects rather than from applied research projects or major program project grants. It would be unfortunate if restrictive legislation hampered the incipient and vulnerable growth phase of this new technology.

Recommendations

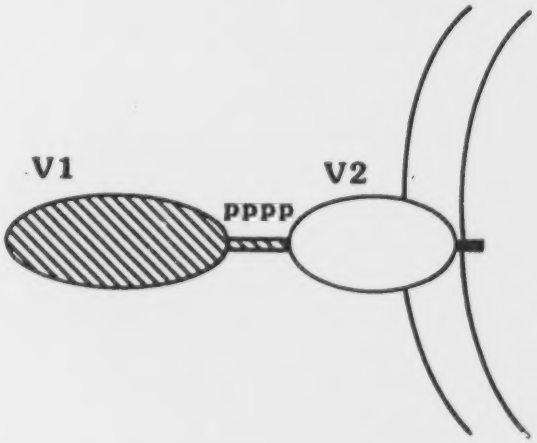
The peer review system must and should be maintained. However, some science funding should be directed toward seed type projects in smaller institutions. New buildings and student training grants can be very helpful for this purpose. The most important research grants are those to individual investigators. More equitable funding could be facilitated by increasing the numbers of such individual grants and reducing the funding of large umbrella-type program project grants.

RAUSCHER SPLEEN FOCUS-FORMING VIRUS ENVELOPE GENE-LTR SEQUENCE

R. Bestwick, B. Boswell and D. Kabat, Department of Biochemistry, Oregon Health Sciences University, Portland, OR 97201

```
                                                                        65
              GCTCATTTACACGCACTCTACCTGGTCCACCACGAAGTCTGCAGACCGTTGGCGGCAGCTTACCA
                                                                       140
ACACCAACTAGACCGGCCGATAGTACCTCACCCTTTCCGACTCGGTGACACAGTGTGGGTCCGCAGGCACCAAAC
                                                                       215
TAACAATCTACAACCCCGTTGCAAAGCACCCTATACCGTCCTCCTGACCACCCCCACCGCTCTCAAAGTAGACGG
            Bam HI                                                     290
CATCGCTGCGTGGATCCACGCCGCTCACGTAAAAGCGGCGACAACCCCTCCGGCCCGAACAGCATCAGGACCGAC
—leader peptide——►                                                     365
ATGGAAGGTCCAGCGTTCTCAAAACCCCTTAAAGATAAGATTAACCCGTGGGGCCCCCTAATAATCCTGGGGATC
METGluGlyProAlaPheSerLysProLeuLysAspLysIleAsnProTrpGlyProLeuIleIleLeuGlyIle
                 ———gp54——►                        cho                  440
TTAATAAGGGCAGGAGTATCAGTACAACATGACAGCCCTCATCAGGTCTTCAATGTTACTTGGAGAGTTACCAAC
LeuIleArgAlaGlyValSerValGlnHisAspSerProHisGlnValPheAsnValThrTrpArgValThrAsn
                      cho                                              515
TTAATGACAGGACAAACAGCTAATGCTACCTCCCTCCTGGGGACAATGACCGATGCCTTTCCTAAACTGTACTTT
LeuMETThrGlyGlnThrAlaAsnAlaThrSerLeuLeuGlyThrMETThrAspAlaPheProLysLeuTyrPhe
                                                                       590
GACTTGTGCGATTTAATAGGGGACGACTGGGATGAGACTGGACTCGGGTCTCGCACTCCCGGGGGAAGAAAAAGG
AspLeuCysAspLeuIleGlyAspAspTrpAspGluThrGlyLeuGlyCysArgThrProGlyGlyArgLysArg
                                                                       665
GCAAGAACATTTGACTTCTATGTTTGCCCCGGGCATACTGTACCAACAGGGTGTGGAGGGCCGAGAGAGGGCTAC
AlaArgThrPheAspPheTyrValCysProGlyHisThrValProThrGlyCysGlyGlyProArgGluGlyTyr
                                                                       740
TGTGGCAAATGGGGCTGTGAGACCACTGGACAGGCATACTGGAAGCCATCATCATCATGGGACCTAATTTCCCTT
CysGlyLysTrpGlyCysGluThrThrGlyGlnAlaTyrTrpLysProSerSerSerTrpAspLeuIleSerLeu
                                                                       815
AAGCGAGGAAACACCCCTCGGAATCAGGGCCCCTGTTATGATTCCTCAGCGGTCTCCAGTGACATCAAGGCCCC
LysArgGlyAsnThrProArgAsnGlnGlyProCysTyrAspSerSerAlaValSerSerAspIleLysGlyAla
                          Eco RI                                       890
ACACCGGGGGGTCGATGCAATCCCCTAGTCCTGCAATTCACTGACGCGCGCAAAAAGGCCAGCTGGGATGCCCCC
ThrProGlyGlyArgCysAsnProLeuValLeuGluPheThrAspAlaGlyLysLysAlaSerTrpAspGlyPro
```

```
                                                                        965
AAAGTATGGGGACTAAGACTATACCGATCCACAGGGACCGACCCGGTGACCCCGTTCTCTTTGACCCGCCAGGTC
LysValTrpGlyLeuArgLeuTyrArgSerThrGlyThrAspProValThrArgPheSerLeuThrArgGlnVal
                                                                       1040
CTCAATATAGGGCCCCGCGTCCCCATTGGGCCTAATCCCGTGATCACTGACCAGTTACCCCCCTCCCGACCCGTG
LeuAsnIleGlyProArgValProIleGlyProAsnProValIleThrAspGlnLeuProProSerArgProVal
                                                                       1115
CAGATCATCCTCCCCAGGCCTCCTCAGCCTCCTCCTCCAGGCGCAGCCTCTATAGTCCCTGAGACTGCCCCACCT
GlnIleMETLeuProArgProProGlnProProProProGlyAlaAlaSerIleValProGluThrAlaProPro
                                                  Bgl I          cho   1190
TCTCAACAACCTCGGACGGGAGACAGGCTGCTAAACCTGGTAGATGGAGCCTACCAGGCACTCAACCTTACCAAC
SerGlnGlnProGlyThrGlyAspArgLeuLeuAsnLeuValAspGlyAlaTyrGlnAlaLeuAsnLeuThrAsn
                                                                       1265
CCTGATAAAACTCAAGATTGCTGGTTATGCCTAGTGTCTCGCACCCCCCTATTACGAGGGGGTTGCTGTCCTAGGC
ProAspLysThrGlnAspCysTrpLeuCysLeuValSerGlyProProTyrTyrGluGlyValAlaValLeuGly
        cho            ←585bp deletion                                 1340
ACTTATTATAATCATACCTCTCCCCTAAAAGAAGAATGTTGTTTCTATGCTGACCATACAGGCCTAGTAAGAGAT
ThrTyrTyrAsnHisThrSerAlaLeuLysGluGluCysCysPheTyrAlaAspHisThrGlyLeuValArgAsp
                                                                       1415
AGTATGGCCAAATTAAGAGAGAGACTCACTCAGAGACAAAAACTATTTGAGTCGAGCCAAGCATGGTTCGAAGAA
SerMETAlaLysLeuArgGluArgLeuThrGlnArgGlnLysLeuPheGluSerSerGlnGlyTrpPheGluGlu
      cho                                                              1490
TTGTTTAACAGATCCACCTGGTTTACCACGTTGATATTCACCATCATAGGGCCTCTCATTATACTCCTACTAATT
LeuPheAsnArgSerThrTrpPheThrThrLeuIlePheThrIleIleGlyProLeuIleIleLeuLeuLeuIle
                                                                       1565
CTGCTTTTTTGGACCCTGCATTCTTAATCAGGATCTCAGTAGTCCAGGCTTTAGTCCTGACTCAACAATACCACC
LeuLeuPheTrpThrLeuHisSer***
                                                          ┌─LTR─→        1640
AGCTAAAACCACTAGAATACGAGCCACAATAAATAAAAGATTTTATTTAGTTTCCAGAAAAAGGGGGGAATGAAC
                                                                       1715
GACCCCACCAAGTTGCTTAGCCTGATAGCCGCAGTAACGCCATTTTGCAAGGCATGGAAAAATACCAAACCAAGA
                                                                       1790
ATAGGGAAGTTCAGATCAAGGTCAGGTGCACGAAAACAGCTAACATTGGGCCAAACAGGATATCTGCGGTGAGCA
                                                                       1865
GTTTCGGCCCCCGGCCCCGGGGCCAAGAACAGATGGTCCCCAGATGTGGCCCAACCCTCAGCAGTTTCTAAAGACCC
                                                    caat box           1940
ATCAGATGTTTCCAGGCTCCCCCAAGGACCTGAAGTGACCCTGTGCCTTATTTGAATTAACCAATCAGCCTGCTT
                                    G/H box                            2015
CTCGCTTCTGTTCGCGCGCTTCTGCTTCCCGAGCTCTATAAAAGAACTCACAACCCCTCACTCGGGCGCCAGTCC
                                    Poly A                             2090
TCCGACAGACTGAGTCGCCCGGGTACCCGTGTATCCAATAAATCCTCTTGCTGTTGCATCCGACTTGTGGTCTCG
                                                    ←LTR─┐
CTGTTCCTTGGGAGGGTCTCCTCAGAGTGATTGACTACCCGTCTCGGGGGGTCTTTCATTTGGGGGCTCGTCCG
```



OSMOTIC OPENING OF THE BLOOD-BRAIN BARRIER TO INCREASE DRUG DELIVERY TO BRAIN TUMOR AND BRAIN ABSCESS

Edward A. Neuwelt, M.D.
Associate Professor Neurosurgery
Assistant Professor Biochemistry
Oregon Health Sciences University
Department of Surgery
Division of Neurosurgery

The lack of response to conventional chemotherapy in patients with malignant brain tumors or brain abscess may be due in part to the presence of the blood-brain barrier (BBB), i.e., tight junctions present between cells that line the blood vessels (capillaries) in the central nervous system (CNS). This barrier prevents most presently available chemotherapeutic agents from reaching the tumors or abscess in high concentration. We are presently continuing our investigation of reversible opening of the blood-brain barrier to increase the delivery of chemotherapeutic agents in animal studies and are employing a clinical trial of intra-arterial methotrexate, intravenous cytoxan and oral procarbazine in patients with malignant brain tumors. We have seen objective response in 15 of 30 patients who have undergone at least three courses of this combination chemotherapy approach. We are also investigating the benefits of BBB modification in several animal models 1) to increase antibiotic delivery to brain infections, 2) to deliver enzymes which may be absent or lacking at birth and 3) to deliver monoclonal antibodies (very specific anti-tumor agents) to brain tumors. These techniques may provide the means to increase the delivery of a multitude of agents to the brain which may be effective in treating a number of terminal illnesses.

Our brain abscess studies are supported by a merit review grant from the Veterans Administration and our brain tumor studies by a grant from the National Institutes of Health.

Biography of Dr. Edward A. Neuwelt

Office Address

Oregon Health Sciences University
Division of Neurosurgery
3181 Southwest Sam Jackson Park Road
Portland, OR 97201

Home Address

4246 S.W. McDonnell Terrace
Portland, Oregon 97201

Date of Birth: May 27, 1948
Place of Birth: Lafayette, Indiana
Marital Status: Married

Education

Northwestern University
Chicago, Illinois
1965 - 1968

University of Colorado School of Medicine
Denver, Colorado
1968 - 1972 - M.D., magna cum laude

Post Graduate Training

University of Texas Southwestern Medical School
Dallas, Texas
1972 - 1973
Internship - Straight Surgical

University of Texas Southwestern Medical School
Dallas, Texas
1973 - 1978
Neurosurgical Residency

Queen Square Hospital
London, England
July, 1976 - December, 1976
Neurosurgical Fellowship

Faculty Appointments

1. University of Texas Southwestern Medical School
   Assistant Professor, Surgery - 1978 - 1981
   Assistant Professor, Biochemistry - 1978 - 1981
   Associate Professor, Surgery - 1981 -

2. Chief, Neurosurgery Service, Dallas V.A. Hospital - 1978 - 1981

3. Attending Staff - Parkland Memorial Hospital - 1978 - 1981
   Children's Medical Center - 1978 - 1981
   St. Paul Hospital - 1980 - 1981

Oregon Health Sciences University

1. Associate Professor Neurosurgery (Dept. of Surgery) - 1981 - Present
   Assistant Professor Biochemistry - 1981 - Present

2. Chief, Neurosurgery Service. Portland V.A. Hospital - 1981 - Present

3. Attending Staff - O.H.S.U. - 1981 - Present

Visiting Professorships

1. Cleveland Clinic - 1979

2. University of Florida, Gainesville - 1982

3. University of Texas, San Antonio - 1983

4. University of Wisconsin, Madison - 1984

5. University of Vienna, Vienna - 1984

6. Karolinska University, Stockholm - 1984

Certification and Licensure

Certified by the American Board of Neurological Surgery
Texas Medical License (License No. E1690)
Oregon Medical License (License No. 31529)

Military Service

United States Public Health Service
Neurosurgery and Enzymology Sections
Baltimore Cancer Research Center
DCT, NCI, NIH
Baltimore, Maryland
July, 1974 - July, 1976
Clinical Associate

Academic Awards

High School
National Honor Society

Northwestern University
Beta Beta Beta Biological Honorary

University of Colorado Medical School
Alpha Omega Alpha Medical Honorary
Gold Reflex Hammer Award in Neurology
Lange Award in Surgery

Professional Societies

Congress of Neurological Surgeons
American Society of Clinical Oncology
American Association Cancer Research
American Association of Neurological Surgeons

Editorial Boards

Editorial board of Neurosurgery

Grants

Subject: Osmotic BBB Opening in Tumor Treatment

Grantor:
NIH - Submitted 1979, not funded; submitted 1980, funded 3 yr ($106,735);
renewal submitted Jan. 1982, not funded; renewal resubmitted June 1983, funded 3 yr ($244,725).
American
Cancer Society - Submitted Oct. 1979, funded 2 yr ($80,000); submitted Oct. 1981, not funded; submitted Nov. 1982, not funded; submitted Nov. 1983, not funded.
Adria Co. - Submitted 1979, not funded.
MRF John Raaf Institute - Submitted May 1982, funded 1 yr ($24,480).
Neurological Sciences Center,
Good Samaritan Hospital - Submitted June 1983, funded 1 yr ($10,000).

Subject: Osmotic BBB Opening in Enzyme Replacement Therapy

Grantor:
March of Dimes - Submitted March 1980, temporarily funded ($10,246); submitted Oct. 1980, not funded.
NIH - Submitted Dec. 1981, not funded.
Tektronix - Submitted Aug. 1983, not funded.

Medical Research
Foundation of Oregon - Submitted Feb. 1983, funded 1 yr ($7,000).

Subject: Osmotic BBB Opening in Brain Abscess Treatment

Grantor:
Veterans Administration - Submitted Dec. 1980, funded 1 yr ($24,864); submitted Merit Review March 1982, funded 2 yr ($80,165); submitted Merit Review Oct. 1983, Funded 3 yr (239,000).
NIH - Submitted Dec. 1981, not funded; submitted Feb. 1982, not funded; submitted Oct. 1983, not funded.

Subject: Autologous Lymphocyte Treatment in Glioma Patients

Grantor:
Assoc. for Brain Tumor Research - Submitted May 1976, not funded.
Veteran's Admin. - Submitted Oct. 1978, funded 1 yr ($24,000).
American Cancer Society - Submitted Oct. 1978, not funded.
Blanche Mary Taxis Foundation - Submitted 1978, funded ($5,000).
Univ. Texas Health Science Center - Submitted July 1978, funded ($4,000).
Southwestern Med Foundation - Submitted Jan. 1979, funded 1 yr ($15,000).
NIH - Submitted April 1980, not funded.
Medical Research
Foundation of Oregon - Submitted May 1981, not funded; submitted Feb. 1982,
funded 1 yr ($12,000).

31 applications submitted, 15 funded (48%) and none pending.

Total funding: $887,215.

Committees

1. President's Advisory Committee on the Biomedical Research Institute - 1982-1983.

2. Public Relations Committee, Congress of Neurologic Surgeons - 1982

3. Neurology Chairman Search Committee - 1983-1984

4. LCME Subcommittee on Research in the School of Medicine - 1983

5. Brain Tumor Committee, Congress of Neurological Surgeons - 1984

6. Sargent at Arms Committee, American Association of Neurological Surgeons - 1984

7. Luncheon Workshop Committee, Congress of Neurological Surgeons - 1984

BIBLIOGRAPHY

Journal Articles

1. Neuwelt E, Stumpf D, Austin J, Kohler P. A monospecific antibody to human sulfatase A preparation, characterization and significance. Biochem Biophys Acta, 236:333-346, 1971.

2. Stumpf D, Neuwelt E, Austin J, Kohler P. Metachromatic leukodystrophy (MLD) X. Immunological studies of the abnormal sulfatase A. Arch Neurol, 25:427-431, 1971.

3. Stumpf D, Neuwelt E, Austin J, Kohler P. Immunological studies of sulfatase A in normals and in metachromatic leukodystrophy. Trans Amer Neurol Assoc, 96:80-83, 1971.

4. Neuwelt E, Stumpf D, Austin J, Kohler P. Recent advances in metachromatic leukodystrophy. In: Symp. On Sphingolipids Sphingolipidoses and Allied Disorders. Volk, B.W. and Aronson, S.M. (eds.) New York, Plenum Plublishing Corp., pp. 415-428, 1972.

5. Neuwelt E, Kohler P, Austin J. Methodolcgy primary enzyme immunoassay (PEIA): studies of the mutant enzyme in metachromatic leukodystrophy (primary enzyme immunoassay of arylsulfatase-A). Immunochem, 10:767-773, 1973.

6. Neuwelt E, Kohler P, Austin J. Immunological studies of the sphingolipidoses. Excerpta Medica, pp. 241-248, 1975.

7. Neuwelt EA, Frank JJ, Levy CC. Purification of human spleen ribonuclease by immunoabsorption: Similarity of the enzyme with human liver ribonuclease. J Biol Chem, 251:5752-5758, 1976.

8. Rosenberg R, Neuwelt E, Kirkpatrick J, Kohler P. Encephalopathy associated with cryoprecipitable australia antigen. Ann Neurol, 1:298-300, 1977.

9. Neuwelt EA, Gahl WA, Levy CC. Immunological studies on the interaction of polyadenylic acid and human liver ribonuclease. Biochem Biophys Res Commun, 73:885-893, 1976.

10. Neuwelt E, Doherty D. Toxicity kinetics and clinical potential of subarachnoid lymphocyte infusions. J Neurosurg, 47:205-217, 1977.

11. Humphrey RL, Karpetsky TP, Neuwelt EA, Levy CC. Levels of serum ribonuclease as an indicator of renal insufficiency in patients with leukemia. Cancer Res, 37:2015-2022, 1977.

12. Neuwelt EA, Schmukler M, Niziak MS, Jewett PB, Levy CC. The immunological characterization of several human ribonucleases by using primary binding tests. Biochem J, 163:419-426, 1977.

13. Neuwelt EA, Garcia JH, Kolar O, Rao K, Ducker T. Elevated CSF gamma globulins with cerebral "glioma". Surg Neurol, 8:107-110, 1977.

14. Neuwelt EA, Boguski MS, Frank JJ, Procter-Appich K, Levy CC. Possible sites of origin of human plasma ribonucleases as evidenced by isolation and partial characterization of ribonucleases from several human tissues. Cancer Res, 38:88-93, 1978.

15. Neuwelt EA, Garcia JH, Mena H. Diffuse microglial proliferation after global ischemia in a patient with aplastic bone marrow. Acta Neuropathol, 43:259-262, 1978.

16. Neuwelt EA, Clark K, Kirkpatrick JB. Preliminary clinical studies of intrathecal autologous lymphocyte infusion in malignant glioma patients. Proc Haemonetics Res Inst Adv Comp Sem, Boston, Massachusetts, 1978.

17. Neuwelt EA, Clark WK. Unique aspects of central nervous system immunology. Neurosurg, 3:419-430, 1978.

18. Neuwelt EA, Clark WK, Kirkpatrick JB, Toben H. Clinical studies of intrathecal autologous lymphocyte infusions in patients with malignant glioma: A toxicity study. Ann Neurol, 4:307-312, 1978.

19. Neuwelt EA, Smith RG. Presence of lymphocyte membrane surface markers on "small cells" in a pineal germinoma. Ann Neurol, 6:133-136, 1979.

20. Neuwelt EA, Glasberg M, Frenkel E, Clark WK. Malignant pineal region tumors: A clinico-pathological study. J Neurosurg, 51:597-607, 1979.

21. Ohata M, Ohno K, Rapoport SI, Pettigrew KD, Fredericks W, Neuwelt EA. Rates of ^{3}H-methotrexate and ^{14}C-sucrose loss from rat brain following enhanced uptake by osmotic opening of blood-brain barrier. Cancer Res, in press, 1984.

22. Samson DS, Neuwelt EA, Beyer CW, Ditmore QM. Failure of extracranial-intracranial arterial bypass in acute middle cerebral artery occlusion: A case report. Neurosurg, 6:185-188, 1980.

23. Neuwelt EA, Maravilla KR, Frenkel EP, Rapoport SI, Hill SA, Barnett PA. Osmotic blood-brain barrier disruption: Computerized tomographic monitoring of chemotherapeutic agent delivery. J Clin Invest, 64:684-688, 1979.

24. Maravilla KR, Neuwelt EA, Diehl JT. Application of metrizamide in the radiographic evaluation of the neurologically diseased patient. Neurosurg, 5:389-406, 1979.

25. Neuwelt EA, Diehl JT, Hill SA, Maravilla KR. Use of metrizamide computerized tomographic cisternography in the evaluation of patients with malignant glioma for immunotherapy. Neurosurg, 5:576-582, 1979.

26. Neuwelt EA, Frenkel EP. Is there a therapeutic role for blood-brain barrier disruption. Ann Int Med, 93:137-139, 1980.

27. Neuwelt EA, Maravilla KR, Frenkel EP, Barnett P, Hill S, Moore RJ. Use of enhanced computerized tomography to evaluate osmotic blood-brain barrier disruption. Neurosurg, 6:49-56, 1980.

28. Neuwelt EA, Frenkel EP, Diehl JT, Maravilla KR, Vu LH, Clark WK, Rapoport SI, Barnett PA, Hill SA, Lewis SE, Ehle AL, Beyer CW, Jr, Moore RJ. Osmotic blood-brain barrier disruption: A new means of increasing chemotherapeutic agent delivery. Trans Am Neurol Assoc, 104:1-5, 1979.

29. Neuwelt EA, Hill SA, Frenkel EP, Diehl JT, Maravilla KR, Vu LH, Clark WK, Rapoport SI, Barnett PA, Lewis SE, Ehle AL, Beyer CW, Jr. Osmotic blood-brain barrier disruption: Pharmacodynamic studies in dogs and a clinical phase I trial in patients with malignant brain tumors. (Third Conference on Brain Tumor Therapy at Asilomar, Monterey, California). Cancer Treat Rep, 65(Suppl #2):39-43, 1981.

30. Neuwelt EA, Frenkel EP, Diehl J, Vu LH, Rapoport S, Hill S. Reversible osmotic blood-brain barrier disruption in humans: Implications for the chemotherapy of malignant brain tumors. Neurosurg, 7:44-52, 1980.

31. Neuwelt EA, Frenkel EP, Rapoport S, Barnett P. Effect of osmotic blood-brain barrier disruption on methotrexate pharmacokinetics in the dog. Neurosurg, 7:36-43, 1980.

32. Neuwelt EA, Batjar HH. Surgical management of pineal region tumors. Contemp Neurosurg, 4(1):1-5, 1982.

33. Neuwelt EA, Frenkel EP, Smith RG. Suprasellar germinomas (ectopic pinealomas): Aspects of immunologic characterization and successful chemotherapeutic responses in recurrent disease. Neurosurg, 7:352-358, 1980.

34. Neuwelt EA, Frenkel EP. Osmotic blood-brain barrier disruption as a means of increasing chemotherapeutic agent delivery to the central nervous system: Animal and clinical studies. In Treatment of Neoplastic Lesions of the Nervous System, J Hildebrand, D Ganghi (eds.), Pergamon Press, Oxford and New York, pp 129-133, 1982.

35. Neuwelt EA, Diehl JT, Long H, Vu LH, Hill SA, Michael AJ, Frenkel EP. Monitoring of methotrexate delivery in patients with malignant brain tumors after osmotic blood-brain barrier disruption. Ann Int Med, 94:449-454, 1981.

36. Neuwelt EA. Use of antibodies and the primary enzyme immunoassay (PEIA) to study enzymes: The arylsulfatase A-anti-arylsulfatase A system. Methods in Enzymology, 73:550-578, 1981.

37. Neuwelt EA. CT monitoring of chemotherapeutic agent delivery after osmotic blood-brain barrier disruption. Clin Neurosurg, 29:520-531, 1980.

38. Watson SW, Sinn DP, Neuwelt EA. Dental considerations in the sublabial trans-sphenoidal surgical approach to the pituitary gland. Neurosurg, 10:236-241, 1982.

39. Neuwelt EA, Glasberg M, Diehl J, Frenkel EP, Barnett P. Osmotic blood-brain barrier disruption in posterior fossa of the dog. J Neurosurg, 55:742-748, 1981.

40. Neuwelt EA, Barringer JA, Brady RO, Pagel M, Furbish FS, Quirk JM, Mook GE, Frenkel E. Delivery of hexosaminidase A to the cerebrum after osmotic modification of the blood-brain barrier. Proc Natl Acad Sci, 78:5838-5841, 1981.

41. Neuwelt EA, Barnett PA, Bigner DD, Frenkel EP. Effects of adrenal cortical steroids and osmotic blood-brain barrier opening on methotrexate delivery to gliomas in the rodent: The factor of the blood-brain barrier. Proc Natl Acad Sci, 79:4420-4423, 1982.

42. Neuwelt EA, Pagel M, Barnett P, Glasberg M, Frenkel EP. Pharmacology and toxicity of intracarotid adriamycin administration following osmotic blood-brain barrier modification. Cancer Res, 41:4466-4470, 1981.

43. Kandalaft N, Diehl J, Neuwelt EA. Nonneoplastic intracranial lesions simulating neoplasms on computed tomographic scan: Excellent sensitivity with limited specificity. JAMA, 248:2166-2168, 1982.

44. Neuwelt EA, Kikuchi K, Hill S, Lipsky P, Frenkel EP. Immune responses in patients with brain tumors: Factors such as anti-convulsants that may contribute to impaired cell-mediated immunity. Cancer, 51:248-255, 1983.

45. Neuwelt EA, Kikuchi K, Hill SA, Lipsky P, Frenkel E. Barbiturate inhibition of lymphocyte function: Differing effects of various barbiturates used to induce coma. J Neurosurg, 56:254-259, 1982.

46. Neuwelt EA, Glasberg M, Frenkel E, Barnett P. Neurotoxicity of chemotherapeutic agents after blood-brain barrier modification: Neuropathological studies. Ann Neurol, 14:316-324, 1983.

47. Neuwelt EA, Hill SA, Kikuchi K. Malignant and benign brain tumors: Current concepts and intervention. Comprehensive Therapy, 9:24-32, 1983.

48. Neuwelt EA, Bigner D, Frenkel EP, Barnett P, Pagel M. Effects of osmotic modification of the blood-brain barrier and adrenal steroid administration on methotrexate delivery to gliomas in rats. Trans Am Neurol Assoc, 106:303-306, 1981.

49. Neuwelt EA, Kikuchi K, Hill SA, Lipsky P, Frenkel E. Differing effects of various barbiturates on lymphocyte function. Trans Am Neurol Assoc, 106:96-98, 1981.

50. Kikuchi K, Neuwelt EA. Presence of immunosuppressive factors in brain tumor cyst fluid. J Neurosurg, 59:790-799, 1983.

51. Neuwelt EA, Barnett P, Barranger J, McCormick C, Pagel M, Frenkel E. Inability of dimethyl sulfoxide and 5-fluorouracil to open the blood-brain barrier. Neurosurg, 12:29-34, 1983.

52. Neuwelt EA, Balaban E, Diehl J, Hill S, Frenkel E. Successful treatment of primary central nervous system lymphomas with chemotherapy after osmotic blood-brain barrier opening. Neurosurg, 12:662-671, 1983.

53. Gumerlock MK, Ono H, Neuwelt EA. Can a patent extracranial-intracranial bypass provoke the conversion of an intracranial arterial stenosis to a symptomatic occlusion? Neurosurg, 12:391-400, 1983.

54. Neuwelt EA, Barranger JA, Pagel MA, Quirk JM, Brady RO, Frenkel EP. Delivery of active Hexosaminidase across the blood-brain barrier in the Rodent. Neurol, in press, 1984. 34:1012; 1984

55. Neuwelt EA, Lewy AJ. Disappearance of plasma melatonin after removal of a neoplastic pineal gland. N Eng J Med, 308:1132-1135, 1983.

56. Neuwelt EA, Specht HD, Howieson J, Haines JE, Bennett MJ, Hill SA, Frenkel EP. Osmotic blood-brain barrier modification: Clinical documentation by enhanced CT scanning and/or radionuclide brain scanning. Am J Neuroradiol, 4:907-913, 1983; and Am J Radiol, 141:829-836, 1983.

57. Neuwelt EA, Rapoport SI. Modification of blood-brain barrier in the chemotherapy of malignant brain tumors. Fed Proc, 43:214-219, 1984.

58. Neuwelt EA, Barnett PA, Glasberg M, Frenkel EP. Pharmacology and neurotoxicity of cis-diamminedichloroplatinum, bleomycin, 5-fluorouracil, and cyclophosphamide administration following osmotic blood-brain barrier modification. Cancer Res, 43:5278-5285, 1983.

59. Neuwelt EA, Barnett PA, Frenkel EP. Chemotherapeutic agent permeability to normal brain and delivery to avian sarcoma virus induced brain tumors in the rodent: Observations on problems of drug delivery. Neurosurg, 14:154-160, 1984.

60. Neuwelt EA, Baker DE, Pagel MA, Blank NK. The cerebrovascular permeability and delivery of gentamicin to normal brain and experimental brain abscess in rodents. J Neurosurg, in press 1983.

61. Neuwelt EA, Hill SA, Frenkel EP. Osmotic blood-brain barrier modification and combination chemotherapy: Concurrent tumor regression in areas of barrier opening and progression in brain regions distant to barrier opening. Neurosurgery, in press, 1984.

62. Neuwelt EA, Frenkel E, Fargion S, Carney D, Minna J, Barnett P. Growth of human lung tumor in the brain and subcutaneous tissues of the nude rat: A new model to evaluate chemotherapy and monoclonal antibody delivery. Cancer Res, in preparation, 1983.

63. Neuwelt EA, Frenkel E, Fargion S, Carney D, Minna J, Barnett P. Delivery of IgM monoclonal antibody, albumin and methotrexate to the CNS after osmotic blood-brain barrier opening. in preparation.

64. Neuwelt EA, Blank N, Johnson WG, Pagel MA, McClure C, Minweiwu P, Kohler R. Characterization of a new animal model of GM-2 gangliosidosis (Sandhoff's disease) in Korat cats. submitted, 1984.

65. Neuwelt EA, Lawrence M, Blank N. The effect of gentamicin and dexamethasone on survival in the rat E. coli brain abscess model with histopathological correlation. in press, 1984.

66. Kikuchi K, McCormick CI, Neuwelt EA. Immunosuppression by phenytoin: Implication for altered immune competence in brain tumor patients. J Neurosurg, in press, 1984.

67. Neuwelt EA, Blank N, Hill SA. The delivery of chemotherapy after blood brain barrier opening: Clinical neuropathological studies. In preparation, 1984.

68. Neuwelt EA, Lawrence M. Clinical and animal studies of amphotericin B delivery to the CNS in association with blood-brain barrier modification. In preparation, 1984.

69. Neuwelt EA, et al. Advances in the diagnosis and treatment of primary CNS lymphoma (microglioma): The role of needle biopsy and blood-brain barrier manipulation. In preparation, 1984.

70. Neuwelt, EA, Barnett P, McCormick C, Frenkel E. Osmotic blood-brain barrier modification: Parameters affecting drug delivery. Proceedings of the 5th International Meeting of the International Society for Developmental Neuroscience, Elesevier. in press, 1984.

71. Neuwelt EA, Minna J, Barnett P, McCormick C, Frenkel E. Pharmacokinetics of monoclonal antibody delivery after osmotic blood-brain barrier modification. In preparation, 1984.

72. Neuwelt EA, Buchan C, Blank NK, Lewy AJ. Surgical resection of a pineal tumor containing elements of germinoma and astrocytoma. Neurosurg, submitted, 1984.

73. Neuwelt EA. An update on the surgical treatment of malignant pineal region tumor. Clinical Neurosurgery. In press, 1984.

Book Chapters

74. Neuwelt EA. Treatment of central nervous system neoplasms. Treatment of Neurological Disease, Rosenberg, R. (ed.), Spectrum Publications, 205-229, 1979.

75. Neuwelt EA, Hill S. Intrathecal lymphocyte infusions: Clinical and animal studies. Neurobiology of Cerebrospinal Fluid, Wood, J. (ed.), Plenum Publishing Company, New York, 525-548, 1980.

76. Neuwelt EA. The role of immunology in the glioma problem. Brain Tumors, Salcman, M. and Hochberg, F. (eds.), Williams and Wilkins Press, In Press.

77. Neuwelt EA. Blood-brain barrier disruption. Neurosurgery, Wilkins, R.H. (ed.), McGraw-Hill Book Co., Part VI, Chapter 130, In press.

78. Neuwelt EA. Opening the blood-brain barrier. Progress in Experimental Brain Tumor Research, Volume II, Rosenblum, M.L. (ed.), S. Karger Publishers, Basel, Switzerland, In press.

Books

79. Neuwelt EA, Clark WK. Clinical Aspects of Neuroimmunology, Williams and Wilkins Press, Baltimore, MD., 1978.

80. Neuwelt EA. (ed). The Diagnosis and Treatment of Pineal Region Tumors, Williams and Wilkins Press, Baltimore, MD. In press, 1984.

Published Abstracts

1. Neuwelt EA, Clark W, Doherty D. Subarachnoid lymphocyte infusion: Toxicity, kinetics and clinical potential. Proc Am Assoc Cancer Res, Abstract No. 37, p. 10, 1977.

2. Neuwelt EA, Clark K. Preliminary clinical studies of intrathecal autologous lymphocyte infusions in malignant glioma patients. Proc Am Soc Clin Oncol, Abstract C-409, p. 409, 1979.

3. Neuwelt EA, Clark WK. Primary malignant pineal region tumors. Proc Am Assoc Neurol Surgeons, Paper No. 12, p. 21, 1979.

4. Neuwelt EA, Clark WK, Frenkel EP. Primary malignant pineal tumors, Proc Am Soc Clin Oncol, Abstract No. C-169, p. 332, 1979.

5. Neuwelt EA, Hill S, Rapoport S, Sheehan R, Mayhood M, Frenkel EP, Kirkpatrick J, Clark WK. Delivery of therapeutic levels of methotrexate to the brain after reversible disruption of the blood-brain barrier. Proc Am Assoc Cancer Res Abstract 397, p. 99, 1979.

6. Neuwelt EA, Clark WK, Frenkel EP. Primary malignant pineal tumors. Intl Symposium Multidisciplinary Aspects Brain Tumor Therapy, Abstract No. A99, 1979.

7. Neuwelt EA. Clinical studies of intrathecal autologous lymphocyte infusions in patients with malignant glioma: A toxicity study. Intl Symposium Multidisciplinary Aspects Brain Tumor Therapy, Gardone Riviera, June 8-10, 1979. Abstract No. A101.

8. Neuwelt EA, Hill SA, Rapoport S, Sheehan R, Mayhood M, Frenkel EP, Kirkpatrick J, Clark WK. Delivery of therapeutic levels of methotrexate to the brain after reversible disruption of the blood-brain barrier. Intl Symposium Multidisciplinary Aspects Brain Tumor Therapy, Gardone Riviera, June 8-10, 1979, Abstract No. 397.

9. Neuwelt EA, Maravilla KR, Rapoport S, Frenkel EP, Hill S, Barnett P. Osmotic blood-brain barrier disruption: Computerized tomographic monitoring of chemotherapeutic agent delivery. 104th Annual Meeting of the American Neurological Association, October 6, 1979, Ann Neurol, 6:166, 1979.

10. Diehl JT, Neuwelt EA, Vu HL. The Demonstration of osmotic blood-brain barrier disruption with contrast enhanced computerized tomography and radionuclide scanning. American Society Neuroradiology, March 16-21, 1980, J Neuroradiol, 1:362, 1980.

11. Neuwelt EA, Diehl J, Hill S, Frenkel E. Osmotic blood-brain barrier disruption in malignant brain tumor patients: A phase I (toxicity) study. Proc Am Soc Clin Oncol, Abstract #C185, p. 365, 1980.

12. Neuwelt E, Frenkel E, Barnett P, Restropo R, Carlson D. Methotrexate (MTX) pharmokinetics after osmotic blood-brain barrier (BBB) disruption. Proc Am Assoc Cancer Res, Abstract #1148, p. 286, 1980.

13. Neuwelt EA, Diehl J, Frenkel EP, Hill S. Osmotic blood-brain barrier disruptions: Implications for the chemotherapy of malignant brain tumors. Texas Medical Association - Section on Neurological Surgery, May 17, 1980.

14. Neuwelt EA, Hill SA. Intrathecal autologous lymphocyte infusions in malignant glioma patients. Meeting of Congress of Neurological Surgeons, October 5-10, 1980.

15. Neuwelt EA, Glasberg M, Frenkel E, Clark WK. Malignant pineal region tumors: A clinico-pathological study. 1981 Year Book on Cancer, in press.

16. Neuwelt EA. Immunotherapy of malignant gliomas. Seventh Annual Richard Lende Winter Neurosurgery Conference, January 31-February 5, 1981.

17. Neuwelt EA, Frenkel EP, Diehl JT, Hill SA. Initial clinical studies of chemotherapy delivery to brain tumor patients after osmotic blood-brain barrier modification. Meeting of the Am Soc Clin Oncol, April, 1981.

18. Neuwelt EA, Diehl J, Glasberg M, Frenkel E, Barnett P. Osmotic blood-brain barrier disruption in the posterior fossa of the canine. American Academy of Neurology, April 27-May 2, 1981, Neurology, 31(2):45, 1981.

19. Neuwelt EA, Barringer J, Brady R, Furbich FS, Pagel M, Frenkel E. Feasibility studies of enhanced hexosaminidase-A delivery to the central nervous system by osmotic blood-brain barrier disruption. American Academy of Neurology, April 27-May 2, 1981, Neurology, 31(2):86, 1981.

20. Glasberg MR, Neuwelt EA, Frenkel EP, Pagel M, Barnett P. Neurotoxicity of adriamycin infusion following osmotic blood-brain barrier disruption in the canine. American Association Neuropathologists, Vancouver, Canada, June 4-6, 1981.

21. Neuwelt EA, Frenkel E, Bigner D. The effects of osmotic modification of the blood-brain barrier and adrenal steroid administration on methotrexate delivery to rodent gliomas. The American Neurological Association Meetings, Ann Neurol, 10:99, 1981.

22. Neuwelt EA, Kikuchi K, Hill S, Lipsky P, Frenkel E. Barbiturate inhibition of lymphocyte function: Differing effects of various barbiturates used to induce coma. American Neurological Association Meetings, Ann Neurol, 10:79, 1981.

23. Neuwelt EA, Frenkel E, Bigner DL, Barnett P. The effects of osmotic modification of the blood-brain barrier and adrenal steroid administration on methotrexate delivery to rodent gliomas. Congress of Neurological Surgeons, Los Angeles, California, October, 1981.

24. Neuwelt EA. Monitoring methotrexate delivery in patients with malignant brain tumors after osmotic blood-brain barrier disruption. Nikko Conference on Brain Tumor Therapy, Nikko, Japan, October 1981.

25. Howieson J, Neuwelt EA. Blood-brain barrier disruption for chemotherapy. 1982 Western Neuroradiological Society Meeting, Stateline, Nevada, March 4-7, 1982.

26. Neuwelt EA, Kikuchi K, Hill SA. Suppression of normal lymphocyte activation by brain tumor cyst fluids. Neurology, 32(2):A146, 1982.

27. Kikuchi K, Neuwelt EA. Suppression of normal lymphocyte activation by brain tumor cyst fluids. Proc Am Soc Clin Oncol, 1:40 (abstract C157), 1982.

28. Neuwelt EA, Kikuchi K, Hill S, Lipsky P, Frenkel EP. Immune responses in patients with brain tumors: factors such as anti-convulsants may contribute to impaired cell-mediated immunity. Proc Am Assoc Cancer Res, 23:249, 1982.

29. Bennett MJ, Steen RR, Neuwelt EA. Anesthesia for disruption of the blood-brain barrier. To be published in Anesthesiol, September, 1982.

30. Neuwelt EA, Lewy AJ. Disappearance of plasma melatonin after surgical removal of a neoplastic pineal gland. Ann Neurol, 12:101, 1982.

31. Neuwelt EA, Frenkel E, Diehl J, Hill S. The Successful use of chemotherapy after osmotic blood-brain barrier disruption in the treatment of microgliomas. Ann Neurol, 12:101, 1982.

32. Neuwelt EA, Frenkel E, Barnett P, McCormick C. Inability of dimethyl sulfoxide (DMSO) and 5-fluorouracil (5-FU) to open the blood-brain barrier to methotrexate and to protein markers. Congress of Neurological Surgeons Meeting, Toronto, Ontario, Canada, October 3-8, 1982.

33. Neuwelt EA, Barranger J, Pagel MA, Brady R, Frenkel E. Delivery of active hexosaminidase across the blood-brain barrier and into sub-cellular organelles of rodent brain cells. AAN Scientific Program. Neurol 33(2):153, 1983.

34. Neuwelt E, Glasberg M, Frenkel E, Barnett P. Neurotoxicity of chemotherapeutic agetns after blood-brain barrier modification: Neuropathologic studies. AACR, 1983.

35. Neuwelt EA, Hill S, Frenkel E. An update on the efficacy of osmotic blood-brain barrier modification in the administration of chemotherapuetic agetns to malignant brain tumor patients. Am Soc Clin Oncol 2:158, 1983.

36. Neuwelt EA, Baker D, Lawrence M, Pagel M, Blank N. Experimental brain abscess: The role of the blood-brain barrier on antibiotic delivery and survival. Neurol 34:137, 1984.

37. Neuwelt EA, Frenkel E, Fargon S, Carney D, Minna J, Hill S, Barnett P, McCormick C. Delivery of tumor-specific monoclonal antibodies to human tumors grown in the nude rat. Neurol 34:184, 1984.

38. Neuwelt E, Blank N, Johnson W, Pagel M, McClure C. Characterization of a new feline model of Sandhoff's disease (GM-2) gangliosidosis. Neurol 34:236, 1984.

Dr. KABAT. Perhaps I could start by saying a few words. I'm David Kabat. My field is cancer research using the tools of molecular biology and recombinant DNA technology. My specific interest is in leukemia which is a cancer that affects blood cells. As you know, cancer cells grow out of control and in the wrong spots in places in the body. And cancer tissue is, therefore, disorganized and abnormal in its overall architecture.

I provided a written statement to the committee. The next to last page of that written statement shows the structure of a cancer gene which we discovered in my laboratory in sequence using recombinant DNA techniques. When that leukemia gene is introduced to normal mouse bone marrow cells, they proliferate wildly.

The last page of that written statement shows a three-dimensional model of the leukemia-causing molecule. The leukemia molecule has a dumbbell shape with two globular regions held together by a flexible coil. Those dumbbell-shaped molecules coat the outer surface membranes of the leukemia cells, and they are the cause for the cell's wild proliferation, and for the death of the affected individual.

What have I learned about science policy and science funding? First thing, I think, is that science is an autocatalytic process. It grows and is enriched and improved where there is existing science because that's where good students are trained, libraries are found, and technical advice can be obtained. Therefore, seed money tends to have an important positive impact, not only on the individual laboratory that receives the funds but also on students and colleagues and recruitment programs throughout the whole institution.

For that reason, I believe, $1 spent on a good research project in a less-developed region of the country can have a more positive impact than $1 spent on an equally good project in an already established research center. As far as I know, there's no provision in the peer review system which takes account of that seed benefit that can accompany the spending of Federal moneys.

Because science is autocatalytic, we see the growth of scientific research centers. The haves tend to acquire and the have-nots may, in some cases, become relatively smaller.

I think the history of biomedical research in this country supports the conclusion that scientific breakthroughs often occur in small institutions far removed from the major research centers. The origin of the Cali-

40-856 O - 85--- 5

fornia Institute of Technology provides one example. Genetic research and the field of biochemical genetics was begun there by scientists who wanted to start a new field far from the dogmas that had dominated their science. Most of Barbara McClintock's Nobel Prize work on jumping genes of corn also was performed alone. Therefore, I think that small institutions must be maintained and strengthened.

I think that certain aspects of the funding system favor the funding of larger research centers. Often peer review committees wonder whether relatively isolated scientists can work effectively. Availability of collaborators is favorably viewed. Such questions about an applicant can easily make the difference between funding or no funding. And also a substantial portion of the research funding has gone to program project and center grants which support large collaborative projects rather than individual grants to investigators. Small institutions have relatively less chance to obtain program project grants.

I think that the peer review system is very important and must be strengthened and maintained; but within its context some science funding can be usefully directed for seed purposes in smaller institutions. New buildings and student training programs are very helpful for that purpose.

And I think, finally, that the most important research grants are those to individual investigators, and that more equitable funding and better science could be facilitated by increasing the proportion of moneys that would be spent on those investigator initiated individual research grants.

Senator HATFIELD. Thank you very much. Dr. Neuwelt?

STATEMENT OF DR. EDWARD NEUWELT

Dr. NEUWELT. Thank you for the opportunity to come and testify. I would like to maybe spend my 2 or 3 minutes talking a little bit about a testimonial. I'm a clinical neurosurgeon at the university and my job is to try and take work that's developed in the laboratory and apply it to taking care of the patient. So rather than discussing the work that we're doing in the laboratory, I would like to mention how the findings that we've developed in the laboratory have helped us take care of the patient.

This is a gentleman—presented to us about 6 months ago from eastern Oregon with a tumor in the brain that can be seen right here as the area of white [indicating]. This tumor is in a very eloquent area of the brain known as the thalamus—an area in the past, as neurosurgeons, we would never want to get into because of too great a danger. With the advent of the CAT scan 10 years ago, we began to be able to see these tumors, but they had a big problem trying to make the diagnosis to be able to treat them properly. Now with the use of the technology from the Space Program, to be able to track very small lesions—or satellites in the outer space, lesions in the brain—we can put needles into these tumors and get small bits of tissue which gives us now for the first time the ability to find out what the basis of the problem is.

With that new technology of getting the tissue we have to learn what to do with it. The amount of tissue that we get is so small that, by standard pathologic techniques, we can't always make the identification of an infection versus a tumor. And that's exactly what happened in this man. This tumor, we got a small piece of tissue from the tumor here [indicating], and this is what it looked like under the microscope. These blue cells, our pathologist said, that they didn't know whether they were inflamatory cells or tumor cells.

Using the advances from the laboratory—using antibodies which are very specific for tumor cells, we were able to use what we call immunohistology, immunopathology, and identify these as malignant lymphocytes, and so-called lymphoma. Now in the past, lymphoma of the brain is different than lymphoma anywhere else in the body. It's particularly common in patients with immunodeficiency disorders, such as AIDS. It's common in patients with transplants. And sometimes it happens in just ordinary people for unknown reasons and only occurs in the brain, does not spread to any other part of the body.

In the past, radiation therapy has been very effective for lymphoma for other parts of the body; but in the brain, you can eliminate the tumor for a very short time, but usually the patient then dies in 9 to 12 months when the tumor comes back. And this is where the technology that we've been developing here in Oregon has been added to this previous technology. We have the technique to open what we call the blood-brain barrier.

Most substances that circulate in the bloodstream are not able to get into the brain because the brain is an electrical organ and it works like a computer. And all the substances that go up and down after meals, if they were able to get into the brain, the brain wouldn't function like a highly efficient computer that it is.

So we have the technique to open this barrier by injecting a drug directly into the artery that feeds that portion of the brain where the tumor is. As you can see here [indicating], normally very few drugs get into the brain. That's the area of blue; very low uptake. We inject our drug to open this blood-brain barrier. In the side where the tumor is, all of a sudden it turns red and white; that means that we've opened the barrier and have gotten enormous amounts of the drug that normally can't get into the brain. What does that mean? Well, that means that this tumor, after two courses of therapy, by first opening the blood-brain barrier and then giving standard chemotherapeutic drugs, the tumor is gone. And now this man has no evidence of a tumor and is walking around eastern Oregon doing very well.

Now how much that's going to prolong his survival, we don't know. But in the past, chemotherapy has had almost no benefit on this kind of malignant brain tumor, and now we have a man who—at least by CAT scan criteria—has no evidence of residual disease. He's one of eight patients with this rare kind of brain tumor which we've had such happy success with.

So I think this is an example of multiple kinds of technology. The CAT scanner, the use of the space age technology to track very small lesions to get a piece of the tissue, use the use of immunology to identify what we have, and now the ability to open the blood-brain barrier and deliver antitumor agents directly to the tumor, which we haven't in the past, are all technological advances which I think that biomedical research, and the funding—all of which is funded by the NIH as well as the Veterans' Administration—has enabled us to do. Thank you.

Senator HATFIELD. Thank you, Dr. Neuwelt. It's a very exciting bit of breakthrough that you share with us today. And Dr. Kabat, we're very grateful for your testimony, too.

STATEMENT OF DR. RICHARD HERSH, VICE PRESIDENT FOR RESEARCH, UNIVERSITY OF OREGON

BIOGRAPHICAL SKETCH

Senator HATFIELD. I would like to invite Dr. Richard Hersh, vice president for research at the University of Oregon in Eugene. Senator Domenici, this is a representative of another of our fine institutions of learning, the University of Oregon. He has a very distinguished record in many fields and in this field of science and research particularly. Dr. Hersh, we're happy to have you here.

[The information follows:]

Biography of Richard H. Hersh

NAME AND ADDRESS:	Richard H. Hersh 4081 Alder Street Eugene, Oregon 97405
BIRTHDATE:	September 5, 1942
PRESENT POSITION:	Vice President for Research University of Oregon Eugene, Oregon 97403
EDUCATION:	Ed.D. - 1969, Boston University (Curriculum and Instruction)
	M.S. - 1965, Syracuse University (Social Science Education)
	B.A. - 1964, Syracuse University (Political Science, History)

PROFESSIONAL EXPERIENCE

January 1980 - January 1984	Dean, Graduate School Associate Provost for Research University of Oregon Eugene, Oregon
July, 1983	D.A.A.D. Fellow Bonn and West Berlin, Germany
August, 1982 - February, 1983	Congressional Fellow Office of Technology Assessment, Washington, D.C.
1976 - 1980	Associate Dean for Teacher Education and Professor of Education, College of Education, University of Oregon Eugene, Oregon
1979	(Summer): Fellow, Center for Advanced Study in the Behavioral Sciences, Stanford University Palo Alto, California
1978	(Summer): Visiting Professor, Western Australia Institute of Technology, Perth, Australia
1975 - 1976	Visiting Professor and Director Center for Moral Development Harvard University Cambridge, Massachusetts
1975 - 1976	Visiting Professor and Director Moral Education Project Ontario Institute for Studies in Education (Concurrent with term at Harvard) Toronto, Ontario (Canada)
1968 - 1975	Professor and Chairman, Secondary Education College of Education, University of Toledo Toledo, Ohio

1966 - 1967	Social Studies Teacher Winchester High School Winchester, Massachusetts
January, 1966 - June, 1966	Social Studies Teacher Lexington High School Lexington, Massachusetts
1965	Teaching Intern Jamesville DeWitt High School Dewitt, New York

BOOKS

Mallan, J. and R. Hersh. NO G.O.D.S IN THE CLASSROOM: INQUIRY INTO INQUIRY. W.B. Saunders Company, Philadelphia. 1972.

Mallan, J. and R. Hersh. NO G.O.D.s IN THE CLASSROOM: INQUIRY AND ELEMENTARY SOCIAL STUDIES. W.B. Saunders Company, Phildelphia. 1972.

Mallan, J. and R. Hersh. NO G.O.D.s IN THE CLASSROOM: INQUIRY AND SECONDARY SOCIAL STUDIES. W.B. Saunders Company, Philadelphia. 1972.

Hersh, R. , et al. PERSPECTIVES IN MORAL AND VALUES EDUCATION. The Ontario Institute for Studies in Education, 1976.

Hersh, R., D. Paolitto, and J. Reimer. PROMOTING MORAL GROWTH; FROM PIAGET TO KOHLBERG. Longman Publishers, New York. 1979. Second edition, 1983.

Hersh, R., J. Miller, and G. Fielding. MODELS OF VALUES AND MORAL EDUCATION AN APPRAISAL. Longman Publishers, New York. January 1980.

Joyce, B., R. Hersh, and M. McKibbin. THE STUCTURE OF SCHOOL IMPROVEMENT. Longman Publishers, New York. 1983.

ARTICLES

Cohen, S. and R. Hersh. "Mirror, Mirror on the Wall," Journal of Teacher Education, Spring 1972.

Hersh, R. and S. Cohen. "A Case Against A Case Against Behavioral Objectives," Elementary School Journal, May 1972.

Cohen, S., and R. Hersh. "Behaviorism and Humanism: A Synthesis," Journal of Teacher Education, Summer 1972.

Hersh, R., and S. Cohen. "Beyond Behavioral Objectives: Individualizing Learning," Elementary School Journal, November 1972.

_____, and F. Buchanan. "Ambiguity and the Nature of Inquiry," Educational Perspectives, Winter 1973.

_____, and C. Gentry. "PBTE: Is It What Broudy Thinks?" AACTE Bulletin, March 1973.

_____, H. Moir and C. Gentry. "An Experiment in Planned Change," American Association of State Colleges and Universities, April 1973.

_____, and D. Merritt. "Changing the Secondary Education Program," Educational Comment (1973) Teacher Education for an Urban Setting. Toledo, College of Education, University of Toledo, 1973.

_____, et al. "Field Testing, Modifying, and Reviewing a Comprehensive Model," Partners for Educational Reform and Renewel, Dickson and Saxe, et al., Berkeley: McCutchan Publishers, 1973.

_____, and J. Whitman. "SOS: Surviving or Surviving," Theory Into Practice, Spring 1974.

_____, and M. Mutterer. "Moral Education and the Need for Teacher Preparation," Values Education: Theory/Practice/Problems/Prospects. (Eds., Meyer, Burnham, and Cholvat) Wilfred Laurier University Press, Waterloo, Onatario, Canada, 1975.

Hersh, R. "PBTE and Multi-Cultural Education: If the Shoe Does Not Fit Should We Wear It?" Sifting and Winnowing: An Exploration of the Relationship Between Multi-Cultural Education and CBTE. (Ed., Carl Grant), Teacher Corps Associates, Madison, Wisconsin, 1975.

_____, J. Mallan and D. Welton. "CTBE: A Dagger in the Mind...?" Social Education, Winter 1976.

_____, and D. Paolitto. "Pedagogical Implications for Stimulating Moral Development in the Classroom," Reflections on Values Education. (Ed., John Meyer). Wilfred Laurier University Press, Waterloo, Ontario, Canada, 1976.

Paolitto, D. and R. Hersh. "Moral Development: Implications for Pedagogy," Contemporary Education, Fall 1976.

Kohlberg, L., and R. Hersh. "Moral Development: A Review of the Theory," Theory into Practice, April 1977.

Hersh, R. "Values and Education: What's It All About?" Teacher Corps 1976: Relections. Expressions. Directions. Washington DC, 1978.

Arends, R., R. Hersh, and J. Turner. "Inservice and the Six O'Clock News," Theory into Practice, June 1978.

Hersh, R., and D. Paolitto. "The Teacher as Moral Educator," Value - Moral Education: The School and the Teachers, edited by Father Thomas Hennessy, Paulist Press, Fall 1978.

Arends, R., R. Hersh and J. Turner. "Conditions for Promoting Effective Staff Development." ERIC Clearinghouse on Teacher Education, Washington DC, 1980

Hersh, R., R. Hull and M. Leighton. "The Nature of Student Teaching," Encyclopedia of Educational Research (5th ed) AERA, Washington DC, 1981

_____, "What Makes Some Schools and Teachers More Effective?" Nexus Vol 4, No. 2, Summer 1982.

_____, "On Bridges, Roads, and Schools: The Infrastructure for Technological Literacy," Bulletin, The American Association for Higher Education, March 1983.

_____, "Are We Becoming A Nation of Technopeasants?" Phi Delta Kappan, May 1983.

_____ "Higher Education and the Corporate Connection," paper presented at the CASE Conference, Spokane, Washington, February 1983.

_____ "Education and the Corporate Connection," Educational Horizons, Pi Lambda Theta, Vol 62, No. 1, Fall 1983.

MONOGRAPHS, REPORTS, BOOK REVIEWS

Hersh, R., "Team Leaders as Teacher Educator," National Teacher Corps Monograph, 1972.

_____, Book review of Values Education Sourcebook in Journal of Moral Education, Vol. 1, No. 1, October 1977.

_____, J. Johnson, and D. Merritt. Second Stage Teachers Center and CBTE Development and Implementation, Part II, Conceptualization and Development of Secondary CBTE, U.S.O.E. Project No. PTR-6221A. Toledo: Center for Educational Research and Sevices, College of Education, University of Toledo, 1974.

_____, and Marcia Mentkowski-Mutterer. "Moral Development and Moral Education: Four Teacher Training Modules," Teacher Corps, Washington DC, 1975.

Fielding, G., and R. Hersh. "Discovering Teacher Centers: The Northwest Passage," Oregon Department of Education supported by U.S.O.E. Teacher Center Documentation Grant, 1979.

_____, and H. Walker. "Research on Effective Schools and Teaching: Implications for Mainstreaming," Paper presented at National Mainstreaming Conference, Summer 1981.

_____, M. Gall, D. Carnine and J. Stockard. "The Management of Education Professionals in Instructionally Effective Schools: Toward A Research Agenda," Paper presented to National Institute of Education, June 1981.

EDITORSHIPS

Hersh, R., editor, "Moral Development," Theory into Practice, April 1977.

_____, editor, "Staff Development/New Perspectives," Theory into Practice, June 1978.

_____, and H. Prehm, editors, Teacher Education and Special Education, Journal of the Teacher Education Division, Council for Exceptional Children, Vol. 1, No. 1, Fall 1977.

_____, North American editor, Journal of Moral Education, 1978 - 1982.

GRANTS AND CONTRACTS

Improving Undergraduate Instruction, National Endowment for the Humanities. To foster greater coherence in the humanities with a program of freshman courses which build more rigorous writing and critical reading standards into small-class contexts. 1983 - 1985.

Humanities and the High School Principal, National Endowment for the Humanities. To reach those individuals in high schools with primary leadership responsibility creating sensitivity and appreciation of humanities and provide basic pedagogy for implementing humanities in their schools. 1984 - 1985.

Minority High School Student Research Apprentice Program, Department of Health and Human Services, to provide experience in various aspects of health-related research for minority high school students, 1981, 1982, 1983.

Teacher Center Grant in collaboration with consortium of school districts, U.S.O.E., To plan, operate and evaluate a Teacher Center, August 1978.

National and Regional Documentation of Teacher Centers, U.S.O.E., To document the progress of Teacher Centers regionally and nationally, August 1978 - 1981.

Dean's Grant, in collaboration with Dean R.G. Gilberts and staff, B.E.H., To plan operate and evaluate a mainstreaming-oriented teacher education program, 1976 - 1979.

Sears, Roebuck Planning Grant, To establish a competency-based secondary teacher education program, University of Toledo, 1972.

Teacher Corps Grants, 1968, 1970, 1972, 1976, 1978.

UNIVERSITY TEACHING

Undergraduate Courses: Social Studies Methods; Teaching Strategies, Curriculum Development; Educational Foundations.

Graduate Courses: Education and the Democratic Ethic; Analysis of Teaching Behavior; Values and Moral Education; Concepts of Teaching; Doctoral Seminar; The Psychology of Curriculum; Inquiry as Instruction

NATIONAL CONFERENCE PRESENTATIONS

National Conference on Family and Education, University of Iowa, February 1981.

National Council of Social Studies, 1969, 1970, 1972, 1974.

American Association of Colleges for Teacher Education, 1972, 1973, 1974, 1976, 1977, 1978, 1979.

Educational Testing Service, National Consortium Development, 1972.

National Teacher Corps Conference, 1971, 1975, 1977, 1978 1979.

American Educational Research Association, 1978, 1979, 1980, 1931, 1982.

Council for Basic Education, Portland, Oregon 1978.

MISCELLANEOUS

Extensive speaking and consultant activity in United States and Canada during past eight years.

Interest in skiing, tennis, racquetball, camping. Previously competed in international rowing competition.

40-856 O - 85 -- 6

Dr. HERSH. Thank you very much. I want to first start out by answering differently the question that Senator Domenici asked earlier about where is new blood coming from in terms of this research.

The Biomedical Research Division of NIH has been sponsoring a program in which they allow high school juniors and seniors to be selected for an Apprenticeship Program. They must be minority students; and the University of Oregon was the university in the State which has participated in that in the last 3 years. There are now nine Oregon students over the last three summers who have spent 8 weeks, 40 hours a week at some minimum wage, but working with our best scientists in their labs. In fact, engaging in some of the forefront research in those labs, as well as doing their own research.

Those students are now in places like Harvard and MIT and Cal Tech and Stanford and several in our own university. And I sit on the panel of NIH that has evaluated this program, and it is overwhelmingly successful, even though the funding has been drastically cut back in the last 3 years.

I would suggest that the data on that program is one wonderful source of support for extending that, not only beyond the minority groups but to any number of students who might consider biomed research as a career, which is a condition of being accepted. And for a relatively small amount of dollars, given what may ultimately come out of even a smaller portion of those people going into biomed research, I suspect that the cost effectiveness would be very, very high.

I'm here to introduce others who can speak more eloquently about the research that we're doing. You should understand the context of the research the University of Oregon is such that we've tried to transcend traditional departments in the way in which we organize research efforts, such that we have institutes. And the people that you'll be hearing from today are members of the Institute for Molecular Biology.

We have institutes of cell biology and neuroscience—at least in the fields that you're interested in today. Those institutes allow us to take faculty members, move them across departments, such that the research they're doing simply obliterates the traditional histories of undergraduate teaching disciplines. Biology and chemistry, for example, are so blurred now that as a teaching device there's a textbook kind of a discipline that may make some sense for catalog and for course numbers, but not for research.

Dr. Novick, who will speak first, is the director of the Institute for Molecular Biology and one of its founders 25 years ago—this is our anniversary of that institute. And in October, as a celebration of that, we'll be having a set of seminars in Eugene at which four Nobel Prize winners will be speaking, including Dr. Watson.

Dr. Capaldi, who will also speak, is department chairman of biology, and will relate to you some of the research that we're doing that has direct impact with regard to people's lives, even though, in fact, the original funding for the research, from NIH and from NSF, was meant to be a basic forefront research but has direct applications to people's lives. Let me let them speak themselves. Thank you very much.

Senator HATFIELD. Thank you, Dr. Hersh. Do you have any questions, Senator?

Senator DOMENICI. I would just ask, Doctor, before you leave, just a couple of observations. It does appear to me that there is a very, very large spectrum from a very young age all the way through college where we have to maintain enthusiasm for our best talent getting into research. We are trying very hard at the national level to reverse some trends.

We just recently passed a math-science enhancement bill, and I think the U.S. House just took it, did they not. So the Senate's version will become law, where we will raise the level of student that is interested in being a teacher of math and science for starters, by giving them some scholarships and giving them some encouragement while they're still in high school; some excellent programs for teachers to remain excited about teaching math, science, physics. And we're speaking of high school and junior high school.

Today we're way up the line, but I think we're beginning to get very worried about the tremendous dropoff in enthusiasm to remain in the educational process as the teachers of the basics: Math, science, engineering concepts, physics. We're going to do our share; and also we're increasing the post doctorate programs in the country dramatically. That's another area that these young, talented people start looking at. Well, I'll go all the way through this, I'll have my doctorate, and I'm still not ready for awhile—and you all know that; you've got to have another 3 or 4 years. There isn't any way for them to make a living.

I think we've just about doubled the post doctorates between NIH and the major labs in the country in the last 18 months and in this last budget. So we're aware that we have to keep the momentum going.

My question was directed more at a very specific thing: Are we more apt to lose the big talent to the big money of medicine, per se, rather than the more exciting but less remunerative profession of research? And I didn't state the question very well, but throughout the course we'll get a few answers from people. Do you have a thought on that?

Dr. HERSH. I do. It just so happens that my own research is about teachers and about schools and about schooling effectiveness. What we know is that what keeps good teachers in teaching is what we call psychic rewards; that is, seeing somebody else learn as opposed to simply increasing salary.

On the other hand, there's a good moral reason for increasing people's salaries at least high enough so they can survive above subsistence. The problem is that the incentive for getting people to go into any field, by putting money into public schools, through scholarships to go into higher education to become teachers, neglects the problem of, that's not so much the incentive as the conditions under which one must go back into those schools to teach. To teach five classes of science to 150 students with, at best, limited equipment to people who don't necessarily want to be in those classes is a condition that no amount of salary would be sufficient to override, No. 1.

No. 2, our experience in seeing high school students come to a university prior to graduating from high school suggests that when they begin to realize that human beings do research and not automans in white coats—people who laugh and who can talk and who are humbled by their own results, people who have intellectual engagement, and people who look like people they know, but who have, in fact, been turned on themselves by something far more than the remuneration of what they think are fat fees for medical things.

That has a profound effect on whether or not they will choose one career or another, at least as they tell us, in their second, third, and fourth years of college having gone through the program. So I maintain that we're talking about both an emotional appeal to people—but only if they can come in contact with the kind of people who are intellectually stimulating. You don't find that very often in American high schools in any subject.

Senator DOMENICI. Mr. Chairman, I tried an experiment in our State and it worked. We asked 12 private sector institutions and labs—18—if they would hire for 2½ months a math and science teacher out of high school, set the stipend for all of them, $500 a week, go there and just go into that institution. And if you're a math teacher, go to Sandia Laboratory and work along side of one of the great mathematicians for $500 a week for summer programs.

We spent no money, no management. We had one of our universities screen the applications; and 44 teachers in math and science got to do that, made $6,000 or $7,000; and every single one wrote back to the administrator that did it for us and said that it was a magnificent experience. They would go back to math and science in the high school with some stories to tell and some enthusiasm.

That's just one little one; but you're saying that's what we have to do across the board in the psychological area. Thank you very much.

Senator HATFIELD. Thank you, Senator Domenici, Dr. Hersh.

STATEMENTS OF:

DR. AARON NOVICK, DIRECTOR, INSTITUTE FOR MOLECULAR BIOLOGY, UNIVERSITY OF OREGON

DR. RODERICK CAPALDI, CHAIRMAN, DEPARTMENT OF BIOLOGY, UNIVERSITY OF OREGON

PREPARED STATEMENTS

Senator HATFIELD. I would like to invite now Dr. Aaron Novick, director of the Institute for Molecular Biology; and Dr. Roderick Capaldi, chairman of the department of biology, both from the University of Oregon. Gentlemen, we will incorporate your full, written statements into the record. And if you care to summarize or highlight that testimony, we would be very pleased to hear from you. Always good to see you, Dr. Novick.

[The statements follow:]

Statement of Dr. Aaron Novick

For the past twenty-five years the Institute of Molecular Biology at the University of Oregon has been a leading center of research in a discipline where discoveries are giving us a deep understanding of the nature of life. Recently, society has discovered that the emerging knowledge also promises powerful and exciting applications, particularly in medicine, but also in many other areas, agriculture among the more prominent.

The science of molecular biology seeks to understand the most basic aspects of life through the properties of proteins and nucleic acids, the two kinds of large molecules (macromolecules) whose characteristics and relationships are the basis of life. All life on earth functions by means of these two kinds of molecules, demonstrating that there is only one type of life on earth.

Proteins form the machinery of life. They serve as the specific catalysts for the myriads of chemical reactions going on in a living organism. They also serve in many other ways, for motion as in muscle, for insulation as in fur or hair, for rigid structure as in horses' hooves, as antibodies which protect us from infecting viruses and bacteria, and in many other ways. All proteins are basically built of a long chain of amino acids which is folded up into a three-dimensional structure. There are the same twenty different kinds of amino acids in all living creatures, and a typical protein chain would have a length of several hundred amino acids. Each type of protein, insulin for example, has its unique arrangement of amino acids.

The "know how" for the assembly of the correct sequence of amino acids in the formation of a particular protein by a living organism is found in its genes. Genes contain this information in nucleic acids, the other type of macromolecule basic to life. Like proteins, nucleic acids are long molecular chains whose individual links are a type of molecule called a nucleotide. There are four types of nucleotides in these chains, and the information in a given nucleic acid is represented by its specific sequence of nucleotides. By analogy with the use by humans of their languages for conveying information, one can think of a nucleic acid expressing a message coded in a language of 4 letters (the nucleotides), where English uses 26 letters.

The discovery of this relationship between proteins and nucleic acid has been followed by a series of discoveries which now make it possible to take a

nucleic acid molecule from one species, e.g., the gene for insulin from a human, and transfer it to a bacterium in which that gene becomes expressed. As a result many medically and commercially valuable proteins such as human insulin and growth hormone are now becoming commercially available. Many other proteins critically important to medicine will become available in the next few years as the new industry of biotechnology expands. The ability to transfer genes between species also promises great benefits in many areas, particularly in agriculture.

Of vital importance in these developments is the ability to control or regulate the expression of the information in a gene in a particular environment. For example, the signals used by a bacterium to promote formation of its proteins from its genes differ significantly from the signals used in human cells. Thus successful expression of the human insulin gene transferred to a bacterium required discovery of the nature of the signals used by the bacteria and tying those signals on to the human insulin gene.

Although research in the Institute has been concerned with every aspect of the molecular basis of life, its primary emphasis has been on how expression of the information in genes is regulated. This line of research is essential to an understanding of how cells differentiate during the development of an individual with billions of cells of different types starting from a single cell, the fertilized egg. Evidently that knowledge is critical to the further development of biotechnology. That knowledge also now assumes great importance in understanding the nature of neoplastic diseases, such as cancer, and, hopefully, in developing a successful therapy or even prevention of these diseases. The uncontrolled growth characteristic of a cancer cell appears to be the consequence of the exaggerated expression of a gene normally present in all cells. The development of the cancer potential in a cell may simply be the result of switching back on a gene used actively in the very earliest period of eukaryotic development and then shut down for the remainder of the animal's life.

The applications of the knowledge generated by the basic research in the Institute are not limited to biotechnology and medicine. One potential comes from a better understanding of how the structure of proteins enables specific function. As noted above, proteins serve many different kinds of uses in living organisms, ranging from mechanical structures to exquisitely specific chemical

catalysts. Each use depends upon the specific structure of a protein. These structures are extremely complex, being composed of thousands of atoms; but they are being elucidated through X-ray diffraction studies aided by high powered computers. The X-ray structure group in the Institute is recognized as one of the best in the world, and collaboration with the groups in genetics and biochemistry in the Institute should develop a deeper understanding of how function depends on structure. It should lead to a technology where proteins can be synthesized to serve specific needs. One can expect a new technological age where proteins will be a source of materials for many present and many new needs.

Another potential comes from the study of cellular membranes and their role in energy generation and in the secretion of proteins by cells. Whether this will lead to a technology of improved photosynthesis is not clear but it certainly must be explored.

The Institute of Molecular Biology was established at the University of Oregon in 1959 to provide a center for research in the then new and rapidly developing field requiring competence in a wide range of disciplines. To facilitate such research the Institute provided a set of contiguous laboratories where faculty from Biology, Chemistry, and Physics could work on related problems, often collaboratively and could share major equipment and administrative services. Faculty members of the Institute hold joint appointments in one of these departments where they do their formal teaching. The Institute enables these faculty to share a common group of graduate students, making it possible for a student from one department to have a Ph.D. research advisor from another department.

The Institute at present is composed of twelve regular members and four associate members; postdoctorals now number 25, with 30 graduate students and 10 research assistants. In addition there are occasional advanced undergraduates who carry out appropriate research projects. Much of the credit for the successful development of the Institute into a leading research center is due to an NSF Centers of Excellence Award given to the University in the mid-1960's. That award provided a substantial amount of the equipment for shared use by the researchers in the Institute; much of that equipment now needs replacement.

The achievements of its staff have brought the Institute international recognition as one of the major research centers in molecular and cellular biology. Its faculty have received many honors. Four of its staff of twelve have been elected to the U.S. National Academy of Sciences, representing the highest concentration of such talent anywhere. Graduate students and post-doctoral fellows come for research training from the very best universities and research institutes.

In recognition of the success of the Institute the most recent session of the Oregon Legislature appropriated specific funds for expansion in molecular and cellular biology. This appropriation will allow the appointment of 4 to 5 new faculty in these areas immediately, and it provides set-up funds for the new faculty as well as for the purchase of limited amounts of shared equipment. An additional two appointments are expected in the next two years by conversion of positions opened by faculty retirements in related areas.

The success of the Institute has led to severe laboratory shortages. Twice the planned number of researchers have been placed in the Institute's laboratory space. Its administrative services, including accounting and budgeting, purchasing, instrument maintenance, and secretarial, have been forced into very crowded inadequate quarters. Effective use of the talents of the Institute staff, and its potential for development calls for at least a doubling in the assigned space.

Research centers of the kind exemplified by the Institute of Molecular Biology are important national resources. When outstanding people work together in a very supportive way on fields of great promise, clearly the whole is much greater than the sum of the parts. The stimulation of colleagues with very high scientific standards when combined with a cooperative and congenial atmosphere greatly increases productivity, both of new knowledge and of new high quality researchers.

STATEMENT OF DR. RODERICK CAPALDI

I am pleased to have the opportunity to testify before the Senate Appropriations Committee on the topic of health related research. The point I wish to make is that BASIC RESEARCH IS A CRITICAL ELEMENT IN OUR MISSION TO

IMPROVE THE HEALTH AND WELL-BEING OF MANKIND and should receive the support it deserves.

It is no exaggeration to say that basic research is the precursor of the applied research that benefits us all in our state of health and quality of life. The revolutionary medical advances of today and amazing technological achievements of this nation in the last few years are the rewards of the basic research conducted 10 or more years ago.

An important consideration in deciding how to support basic research is the unpredictability of where basic research might lead. One could not have expected Fleming's work with bacterial growth to lead to the discovery of penicillin. Similarly, it could not have been foreseen that progress in understanding molecular magnetism and advances in computer technology would lead to development of a truly amazing diagnostic tool, the "whole body" nuclear magnetic resonance spectrophotometer. This instrument allows visualization of the metabolic processes going on in our bodies, and is non-invasive and thus potentially much safer than other available approaches for examining organic disease.

The above examples are two of a multitude that show how basic research in an unrelated area has improved the health of mankind. Another example is the development of the methods now known as biotechnology by which important drugs such as human insulin and growth hormone can be manufactured in large amounts by bacterial or fungal fermentations. It is the body of knowledge obtained from basic research as a whole which is the critical foundation on which research applied to specific health problems is based.

There are several important research projects at the University of Oregon that can serve as useful examples of the importance of basic research. Several of my colleagues are working on the way in which proteins bind to the genetic material DNA in order to determine which genes are read and which are not. Their research focuses on such basic questions as the way in which proteins recognize particular sequences of the building blocks of the DNA and the nature of the binding of proteins to the DNA structure itself. This research is aimed at a fundamental understanding of these processes. None of the projects by themselves is likely to provide a magic bullet to cure any disease. However, an understanding at the molecular level of how genes are

turned on or off may aid in developing anti-cancer drugs and may ultimately lead to a better understanding of birth defects.

Another example of how a body of basic knowledge can aid in combatting health problems when developed far enough comes from my own research. My interest is in how our cells convert the energy available in the foodstuffs we eat into usable energy for growth and reproduction, and for other cellular functions such as muscle action. The present level of understanding of this process called oxidative phosphorylation has been built up by a large number of laboratories over a time span of 20 years. My colleagues and I have contributed to the identification of the individual proteins in cells which act as the catalysts that burn the food materials by reacting them with the oxygen we breathe. This liberates the energy in the chemical bonds between atoms in the food materials. This energy is then trapped in a useful form for cellular process, as a chemical called adenosine triphosphate or ATP. We are now beginning to map the juxtapositions of the proteins involves in oxidative phosphorylation in the cell.

There are several human diseases in which the cell's ability to make or use ATP is affected. I have recently had the opportunity to help in the diagnosis and treatment of one group of such metabolic diseases by contributing the basic knowledge I have obtained in my own research. The first instance involved a patient referred to Dr. Neil Buist, a consultant and Director of the Pediatric Metabolism Laboratory at the University of Oregon Health Sciences University in Portland. This patient presented with debilitating muscle weakness and fatigue and with bouts of low blood pH due to build-up of lactic acid in the muscle and bloodstream. Dr. Buist and his colleagues had ruled out several possible metabolic defects and were drawn to the conclusion that the problem might involve the enzymes of oxidative phosphorylation. Beyond this, precise diagnosis was not possible because of inadequate techniques for examining the proteins involved in this process. He contacted me as a local person involved in basic research on the mechanism of oxidative phosphorylation. We were able to adapt approaches I had developed in my own basic research to check for the presence of these enzymes in the muscle tissue of the patient. We were able to make a precise diagnosis: that one of the key proteins in providing the muscle cells with energy was missing.

Once we knew what was missing, we were able to devise a therapeutic regimen which, in effect, bypasses the missing protein. The patient is now significantly recovered and able to take considerably more physical exertion than before. As a result of this success, the Medical School in Portland is becoming a center for referral for patients with diseases in Oxidative Phosphorylation, a condition known as Mitochondrial Myopathy.

In summary, I believe it is essential to support basic research and at a level above that done now. As a member of Peer Review Panels at the National Institutes of Health I see many deserving research projects that go unfunded. Evaluation of the merits of basic research projects should be made on the criterion of excellence of ideas and competence of investigators. As I have tried to explain, it is difficult to predict whether a given piece of basic research will lead to useful applications. Funding of a broad range of basic research projects is an important counterpoint to the more narrowly focused missions of the different National Institutes of Health.

Biography of Dr. Roderick Capaldi

TITLE: Professor of Biology
Member, Institute of Molecular Biology

ADDRESS: Institute of Molecular Biology
University of Oregon
Eugene, Oregon 97403

BIRTHDATE AND PLACE: May 5, 1944
Knaresborough, Yorkshire, England

NATIONALITY: British, Immigration Visa

EDUCATION:

1967	B.Sc.	University of London, England Botany, Zoology, Chemistry
1970	D. Phil.	University of York, England Chemistry

HONORS AND/OR PROFESSIONAL EXPERIENCE:

1970-1972	Research Associate, in Dr. David E. Greens' Laboratory, Institute of Enzyme Research, University of Wisconsin, Madison, Wisconsin
1972-1973	Assistant Research Professor, Institute of Enzyme Research, University of Wisconsin, Madison, Wisconsin
1973-1978	Assistant Professor of Biology and Member of the Institute of Molecular Biology, University of Oregon, Eugene, Oregon

1977-1982	Established Investigator, American Heart Association
1978-1981	Associate Professor of Biology and Member of the Institute of Molecular Biology, University of Oregon, Eugene, Oregon
1981-Present	Professor of Biology and Member of the Institute of Molecular Biology, University of Oregon, Eugene, Oregon
1984-Present	Head, Department of Biology, University of Oregon, Eugene, Oregon

PUBLICATIONS

Roderick A. Capaldi

1. Capaldi, R.A. and C.J. Carratt. An analysis of a structural difference between beef and pork insulin detected by differences in the exchange rates of amide hydrogens as measured by infrared spectroscopy. Eur. J. Biochem. 23, 551-556 (1971).

2. Capaldi, R.A. and G. Vanderkooi. The low polarity of many membrane proteins. Proc. Natl. Acad. Sci. USA 69, 930-932 (1972).

3. Vanderkooi, G. and R.A. Capaldi. A comparative study of the amino acid compositions of membrane proteins and other proteins. Ann. N.Y. Acad. Sci. 195, 135-138 (1972).

4. Vanderkooi, G., Senior, A.E., Capaldi, R.A. and H. Hayashi. III. The lattice structure of membranous cytochrome oxidase. Biochim. Biophys. Acta 274, 38-48 (1972).

5. Capaldi, R.A. The structure of erythrocyte membranes. A partial separation of intrinsic and extrinsic membrane proteins. Eur. J. Biochem. 29, 74-79 (1972).

6. Hayashi, H. and R.A. Capaldi. The proteins of the outer membrane of beef heart mitochondria. Biochim. Biophys. Acta 282, 166-173 (1972).

7. Capaldi, R.A. and D.E. Green. Membrane proteins and membrane structure. FEBS Letters 25, 205-209 (1972).

8. Hayashi, H., Vanderkooi, G. and R.A. Capaldi. On the stability of the lattice structure of membranous cytochrome oxidase. Biochem. Biophys. Res. Commun. 49, 92-98 (1972).

9. Capaldi, R.A. and H. Hayashi. The polypeptide composition of cytochrome oxidase from beef heart mitochondria. FEBS Letters 26, 261-263 (1972).

10. Jost, P.C., Griffith, O.H., Capaldi, R.A. and G. Vanderkooi. Evidence for boundary lipid in membranes. Proc. Natl. Acad. Sci. USA 70, 480-484 (1973).

11. Capaldi, R.A. A hydrogen-deuterium exchange study of membranous cytochrome oxidase. Biochim. Biophys. Acta 303, 237-241 (1973).

12. Capaldi, R.A. A cross linking study of the beef erythrocyte membrane: Extensive interaction of all the proteins of the membrane except for the glycoproteins. Biochem. Biophys. Res. Commun. 50, 656-661 (1973).

13. Komai, H. and R.A. Capaldi. On the subunit structure of cytochrome oxidase from beef heart mitochondria. FEBS Letters 30, 273-276 (1973).

14. Maniloff, J., Vanderkooi, G., Hayashi, H. and R.A. Capaldi. Optical analysis of electron micrographs of cytochrome oxidase membranes. Biochim. Biophys. Acta 298, 180-183 (1973).

15. Capaldi, R.A. Properties of the major glycoprotein of the beef erythrocyte membrane. Biochim. Biophys. Acta 311, 386-390 (1973).

16. Jost, P., Griffith, O.H., Capaldi, R.A. and G. Vanderkooi. Identification and extent of fluid bilayer regions in membranous cytochrome oxidase. Biochim. Biophys. Acta 311, 141-152 (1973).

17. Capaldi, R.A. On the subunit structure of oligomycin sensitive ATPase. Biochem. Biophys. Res. Commun. 53, 1331-1337 (1973).

18. Griffith, O.H., Jost, P., Capaldi, R.A. and G. Vanderkooi. Boundary lipid and fluid bilayer regions in cytochrome oxidase model membranes. Ann. N.Y. Acad. Sci. 222, 561-573 (1973).

19. Jost, P.C., Capaldi, R.A., Vanderkooi, G. and O.H. Griffith. Lipid-protein and lipid-lipid interactions in cytochrome oxidase model membranes. J. Supramolecular Structure 1, 269-280 (1973).

20. Capaldi, R.A., Komai, H. and D.R. Hunter. Isolation of a major hydrophobic protein of the mitochondrial inner membrane. Biochem. Biophys. Res. Commun. 55, 655-659 (1973).

21. Capaldi, R.A. A dynamic model of cell membranes. Sci. American 230, 26-33 (1974).

22. Capaldi, R.A. Identification of the major enzymic activities of the mitochondrial inner membrane in terms of their migration in sodium dodecyl sulfate polyacrylamide gel electrophoresis. Arch. Biochem. Biophys. 163, 99-105 (1974).

23. Hunter, D.R. and R.A. Capaldi. Respiratory control in cytochrome oxidase. Biochem. Biophys. Res. Commun. 56, 623-628 (1974).

24. Capaldi, R.A. and M. Briggs. The structure of cytochrome c oxidase. In "Membrane Bound Enzymes," A. Martonosi, ed., Butterworths and Co., London, pp. 87-102 (1976).

25. Briggs, M., Kamp, P-F., Robinson, N. and R.A. Capaldi. The subunit structure of the cytochrome c oxidase complex. Biochemistry 14, 5123-5128 (1975).

26. Bell, R.L. and R.A. Capaldi. The polypeptide composition of ubiquinone-cytochrome c reductase (Complex III) from beef heart mitochondria. Biochemistry 15, 996-1001 (1975).

27. Downer, N.W., Robinson, N.C. and R.A. Capaldi. Characterization of a seventh different subunit of beef heart cytochrome c oxidase. Similarities between the beef heart enzyme and that from other species. Biochemistry 15, 2930-2936 (1976).

28. Capaldi, R.A. Mitochondiral membrane structure. In "Mammalian Cell Membranes," G.A. Jameson and D.M. Robinson, eds., Butterworths and Co., London, vol 2, pp. 141-164 (1977)

29. Briggs, M. and R.A. Capaldi. Near neighbor relationships among the subunits of cytochrome c oxidase. Biochemistry 16, 73-78 (1977).

30. Robinson, N.C. and R.A. Capaldi. Interaction of detergents with cytochrome c oxidase. Biochemistry 16, 375-380 (1977).

31. Capaldi, R.A., Bell, R.L. and T. Branchek. Changes in order of migration of polypeptides in complex III and cytochrome c oxidase under different conditions of SDS polyacrylamide gel electrophoresis. Biochem. Biophys. Res. Commun. 74, 425-433 (1977).

32. Capaldi, R.A. Membrane proteins and membrane structure. In "Membrane Proteins and their Interactions with Lipids," R.A. Capaldi, ed., Marcel Dekker, New York, pp. 1-15 (1977).

33. Smith, R.J. and R.A. Capaldi. Nearest neighbor relationships of the polypeptides in ubiquinone cytochrome c reductase (Complex III). Biochemistry 16, 2629-2633 (1977).

34. Henderson, R., Capaldi, R.A. and J.S. Leigh. Arrangement of cytochrome oxidase molecules in two-dimensional vesicle crystals. J. Mol. Biol. 112, 631-648 (1977).

35. Ball, M.B., Bell, R.L. and R.A. Capaldi. Trypsin cleavage of ubiquinone cytochrome c reductase complex III. FEBS Letters 83, 1, 99-102 (1977).

36. Capaldi, R.A., Sweetland, J. and A. Merli. Polypeptides in the succinate coenzyme Q reductase segment of the respiratory chain. Biochemistry 16, 5707-5710 (1977).

37. Vik, S. and R.A. Capaldi. Lipid requirements for cytochrome c oxidase. Biochemistry 16, 5755-5759 (1977).

38. Longmuir, K.H., Capaldi, R.A. and F.W. Dahlquist. NMR studies of lipid-protein interactions in cytochrome c oxidase. Biochemistry 16, 5746-5755 (1977).

39. Ackrell, B.A.C., Kearney, E.B., Merli, A., Ludwig, B. and R.A. Capaldi. Interactions between succinate dehydrogenase and its membrane environment. In "Mechanisms of Oxidizing Enzymes," T.P. Singer and O. Ondarza eds., Elsevier, North Holland, pp. 143-154 (1978).

40. Briggs, M.M. and R.A. Capaldi. Cross linking studies on a cytochrome c - cytochrome c oxidase complex. Biochem. Biophys. Res. Commun. 80, 553-559 (1978).

41. Smith, R.J., Capaldi, R.A., Muchmore, D. and F.W. Dahlquist. Cross linking of ubiquinone cytochrome c reductase (complex III) with periodate-cleavable bifunctional reagents. Biochemistry 17, 3719-3723 (1978).

42. Bell, R.L., Sweetland, J., Ludwig, B. and R.A. Capaldi. Labelling of complex III with [^{35}S] DABS: Orientation of this electron transfer segment in the mitochondrial inner membrane. Proc. Natl. Acad. Sci. USA 76, 741-745 (1979).

43. Merli, A., Capaldi, R.A., Ackrell, A.C. and E.B. Kearney. Arrangement of complex II (succinate-ubiquinone reductase) in the mitochondrial inner membrane. Biochemistry 18, 1393-1400 (1979).

44. Ludwig, B., Downer, N.W. and R.A. Capaldi. Labelling of cytochrome c oxidase with [^{35}S] diazobenzenesulfonate. Orientation of this electron transfer complex in the inner mitochondrial membrane. Biochemistry 18, 1401-1407 (1979).

45. Ludwig, B. and R.A. Capaldi. Immunoprecipitation of ATP synthetase from beef heart mitochondria. Biochem. Biophys. Res. Commun. 87, 1159-1167 (1979).

46. Fuller, S.D., Capaldi, R.A. and R. Henderson. Structure of cytochrome c oxidase in deoxycholate-derived two dimensional crystals. J. Mol. Biol. 134, 305 (1979).

47. Ludwig, B., Prochaska, L. and R.A. Capaldi. Arrangement of oligomycin-sensitive adenosine triphosphatase in the mitochondrial inner membrane. Biochemistry 19, 1516-1523 (1980).

48. Vik, S.B. and R.A. Capaldi. Conditions for optimal electron transfer activity of cytochrome c oxidase isolated from beef heart mitochondria. Biochem. Biophys. Res. Commun. 94, 348-354 (1980).

49. Prochaska, L., Bisson, R. and R.A. Capaldi. Structure of the cytochrome c oxidase complex: Labeling by hydrophilic and hydrophobic protein modifying reagents. Biochemistry 19, 3174-3179 (1980).

50. Bisson, R., Jacobs, B. and R.A. Capaldi. Binding of arylazidocytochrome c derivatives to beef heart cytochrome c oxidase: Cross-linking in the high- and low-affinity binding sites. Biochemistry 19, 4173-4178 (1980).

51. Girdlestone, J., Bisson, R. and R.A. Capaldi. Interaction of succinate-ubiquinone reductase (complex II) with (arylazido) phospholipids. Biochemistry 20, 152-156 (1981).

52. Vik, S.V., Georgevich, G. and R.A. Capaldi. Diphosphatidylglycerol is required for optimal activity of beef heart cytochrome c oxidase. Proc. Natl. Acad. Sci. USA 1456-1460 (1981).

53. Bisson, R. and R.A. Capaldi. Binding of arylazidocytochrome c to yeast cytochrome c peroxidase. J. Biol. Chem. 256, 4362-4367 (1981).

54. Prochaska, L.J., Bisson, R., Capaldi, R.A., Steffens, G.C.M. and G. Buse. Inhibition of cytochrome c oxidase function by dicyclohexydlcarbodiimide. Biochim. Biophys. Acta 637, 360-373 (1981).

55. Capaldi, R.A., Darley-Usmar, V., Fuller, S.D. and G. Georgevich. Structure and functioning of cytochrome c oxidase in "Vectorial Reaction in Electron and Ion Transport in Mitochondria and Bacteria" (F. Palmieri, E. Quagliariello, N. Siliprandi and E.C. Slater, eds.) pp. 25-35, Elsevier North Holland (1981).

56. Fuller, S.D., Darley-Usmar, V.M. and R.A. Capaldi. Covalent complex between yeast cytochrome c and beef heart cytochrome c oxidase which is active in electron transfer. Biochemistry 20, 7046-7053 (1981).

57. Darley-Usmar, V.M., Capaldi, R.A. and M.T. Wilson. Identification of cysteines in subunit II as ligands to the redox centers of bovine cytochrome c oxidase. Biochem. Biophys Res. Commun. 103, 1223-1230 (1981).

58. Georgevich, G. and R.A. Capaldi. Cytochrome c oxidase-lipid interface from the protein side. Biophys. J. 37, 66-67 (1982).

59. Capaldi, R.A., Darley-Usmar, V., Fuller, S. and F. Millett. Structure and functional features of the interaction of cytochrome c with complex III and cytochrome c oxidase. FEBS Lett. 138, 1-7 (1982).

60. Capaldi, R.A., Prochaska, L. and R. Bisson. Structure of cytochrome c oxidase. In "Electron Transport and Oxygen Utilization" Chien Ho ed., Elsevier, North Holland, pp. 139-144 (1982).

61. Capaldi, R.A. Structure of intrinsic membrane proteins. Trends in Biochemical Science 7, 292-295 (1982).

62. Deatherage, J.D., Henderson, R. and R.A. Capaldi. Three dimensional structure of cytochrome oxidase vesicle crystals in negative stain. J. Mol. Biol. 158, 487-499 (1982).

63. Deatherage, J.D., Henderson, R. and R.A. Capaldi. Relationship between membrane and cytoplasmic domains in cytochrome c oxidase by electron microscopy in media of different density. J. Mol. Biol. 158, 501-514 (1982).

64. Fuller, S.D., Capaldi, R.A. and R. Henderson. Preparation of two dimensional arrays from purified beef heart cytochrome c oxidase. Biochemistry 21, 2525-2529 (1982).

65. Millett, F., Darley-Usmar, V. and R.A. Capaldi. Cytochrome c oxidase is cross-linked to subunit II of cytochrome c oxidase by a water-soluble carbodiimide. Biochemistry 21, 3857-3862 (1982).

66. Bisson, R., Steffens, G.C.M., Capaldi, R.A. and G. Buse. Mapping of the cytochrome c binding site on cytochrome c oxidase. FEBS Lett. 144, 359-363 (1982).

67. Capaldi, R.A., Prochaska, L. and R. Bisson. Structure of cytochrome c oxidase. In "Electron Transport and Oxygen Utilization" (C. Ho, ed.) pp. 139-144 (1982).

68. Capaldi, R.A., Marshall, F.A. and S.J. Staples. Structure of membrane proteins and their amino acid sequences. Comments on Mol. and Cell Biophysics 1, 365-379 (1982).

69. Capaldi, R.A. Arrangement of proteins in the mitochondrial inner membrane. Biochim. Biophys. Acta 694, 291-306 (1982).

70. Malatesta, F. and R.A. Capaldi. Localization of cysteine 115 in subunit III of beef heart cytochrome c oxidase to the C side of the mitochondrial inner membrane. Biochem. Biophys. Res. Commun. 118, 1180-1185 (1982).

71. Millett, F., deJong, C., Paulson, L. and R.A. Capaldi. Identification of specific carboxylate groups on cytochrome c oxidase that are involved in binding cytochrome c. Biochemistry 22, 546-552 (1983).

72. Georgevich, F., Darley-Usmar, V.M., Malatesta, F. and R.A. Capaldi. Electron transfer in monomeric forms of beef and shark heart cytochrome c oxidase. Biochemistry 22, 1317-1322 (1983).

73. Capaldi, R.A., Malatesta, F. and V.M. Darley-Usmar. Structure and function of cytochrome c oxidase. Biochim. Biophys. Acta 726, 135-148 (1983).

74. Darley-Usmar, V.M., Kennaway, N.G., Buist, N.R.M. and R.A. Capaldi. Deficiency in ubiquinone cytochrome c reductase in a patient with mitochondrial myopathy and lactic acidosis. Proc. Natl. Acad. Sci. USA 80, 5103-5106 (1983).

75. Malatesta, F., Darley-Usmar, V.M., deJong, C., Prochaska, L.G., Bisson, R., Capaldi, R.A., Steffens, G.C.M. and G. Buse. Arrangement of subunit IV in beef heart cytochrome c oxidase probed by chemical labeling and protease digestion experiments. Biochemistry 22, 4405-4411 (1983).

76. Malatesta, F., Georgevich, G. and R.A. Capaldi. Structural studies on beef heart cytochrome c oxidase from which subunit III has been removed by chymotrypsin treatment. In Structure and Function of Membrane Proteins (E. Quagliariello and F. Palmieri, eds.), Elsevier Science Publishers, pp. 223-235 (1983).

77. Darley-Usmar, V.M., Georgevich, G. and R.A. Capaldi. Reaction of thionitrobenzoate-modified yeast cytochrome c with monomeric and dimeric forms of beef heart cytochrome c oxidase. FEBS Lett. 166, 131-135 (1984).

78. Lötscher, H.R. and R.A. Capaldi. Structural asymmetry of the F_1 of Escherichia coli as indicated by reaction with dicyclohexylcarbodiimide. Biochem. Biophys. Res. Commun. 121, 331-339 (1984).

STATEMENT OF DR. AARON NOVICK

Dr. NOVICK. Thank you, Senator Hatfield. I'm happy to be here. Thank you, Senator Domenici.

Senator Hatfield, I would like to begin by saying that the Institute of Molecular Biology was founded at the University of Oregon the same day you began your first term as Governor of this State. In fact—I'm sure you don't recall this—at one point I came to you with some idea about developing further and you were very supportive. Finally, a large grant from the National Science Foundation, the Centers of Excellence award, played a critical role in our development and our success. We are one of the first three universities of the United States to receive one of these awards.

I would like to also second the things you have heard from President Laster and Professor Herbert and the others about the promise for medicine, and industry too, with the developments in molecular biology.

In reality, a revolution has occurred as we develop a deep understanding of what is life. In fact, we see that life is fundamentally a relationship between proteins and nucleic acids—proteins forming the machinery, ranging from the hooves of a horse to the most sophisticated enzymes involved in our brains. And it's this relationship—the breakthrough occurred in understanding this relationship roughly 30 years ago. And that coincided, really, with the development of our institute during which time people began to understand first, that the information for the structure of proteins is coded in genes in the form of something called nucleic acids.

Some of the work done at the University of Oregon had to do with the punctuation of that genetic code, how it's read. But our major interest has been in how genes are regulated.

This, finally, is the interesting question. We understand very well how the information is coded, but how it is regulated is now the current question. It would enable us to understand how a single fertilized egg develops into the complex creatures with many millions or billions of cells such as ourselves. But also, as you have heard, it has extremely important implications toward understanding the nature of cancer and its treatment. And as you heard, great progress is occurring here.

But our institute has dealt with the fundamental aspects. We have, I'm proud to say, accumulated a very distinguished staff. Out of our 12 members, 4 have been elected to the U.S. National Academy of Sciences. And that concentration of outstanding scientists, I think, is unique in the country. I'm very sad to report that one of them, Professor George Streisinger, died just 10 days ago—heart attack while being certified as a scuba diver. George was one who went in for—his science and life in general is one of thrills and adventure and reminds one that the best science that is done is fun and adventurous.

Our groups really deal in a number of levels. Some are directly controlled with how genes are expressed, the biological and genetic level. We have others who, like Professors Von Hipple and Mathews, were

40-856 O - 85 -- 7

concerned with the detailed physical and chemical mechanisms involved.

And then we have others, like Professor Capaldi, Professor Stevens, who are concerned with how genes are expressed.

I would like to add one thing: In addition to the applications to medicine that you've heard about—prevention and treatment—there are going to be a lot of other applications we haven't imagined yet. But I can even see applications to industry.

Life uses proteins, as I said, ranging from the material to make a horse's hoof to the most subtle molecules in our bodies. As we understand the relationship between the structure of proteins and their functions, we'll not only be able to design enzymes for industrial catalysts that are much better than anything we have today, we'll probably, I would predict, have a new materials science using proteins for a wide variety of human purposes. That's a prediction. It may not come next year, but I'm convinced that it will occur within 20 years.

Well, this has been an exciting time for us, and I'm delighted to see the Health Sciences University enter this field, as I think the rewards are very great. Thank you.

Senator HATFIELD. Thank you, Dr. Novick. Dr. Capaldi?

STATEMENT OF ROD CAPALDI

Dr. CAPALDI. I'm Rod Capaldi, a member from the Institute of Molecular Biology and a member of the biology department head. The thrust of my written testimony was an argument in favor of the role of basic research in terms of its application, as the broadness of basic research is the way to develop a body of information around which ultimately the applied research and the development of treatments for specific diseases arises. And so I leave that as the record, and I would like to take just the few minutes I have to identify and describe for you one way in which basic research actually comes to fruition in terms of looking at disease states. And it happens to be a piece of research that I've been involved with. It turns out to have many of the facets that we've heard in other testimony in the sense of being an endeavor that involves some basic research. It involves the clinician; and it involves a very exciting new technology. Just to give it some background, my own research is in the way our cells—and in particular, our heart cells—are able to convert energy from one form to another. As you know, we take in our energy in the form of food materials which are broken down eventually into the cells that are actually burned using molecular oxygen. And we convert that energy that we get from the chemical bonds in our food materials into a form of energy our cells can use, called ATP.

And over the last 10 years or so at Oregon, I've been interested in the sort of proteins and enzymes that are involved in that process. And I've studied them at the level of the basic research, trying to understand how would such an enzyme work. And now to come in from the other direction, clinicians at the medical school here in Portland are involved

in a very active program in pediatric metabolism. And of the physicians there, Dr. Buist, who sees more and more frequently new patients that have diseases that manifest at the beginning like muscular dystrophy but clearly cannot be muscular dystrophy.

And the pathological analysis suggests that there's something wrong with mitochondria, which are a part of the cell that are involved in converting energy—the sort of work that I'm interested in.

Dr. Buist knew of my basic research and contacted me 2 years ago with respect to one specific patient. Here was an example of a clinician who was up on the basic research and identified a person that he could consult with respect to how he might go further in the diagnosis of this particular patient's problem.

Briefly, the patient was suffering from low blood pH due to a build-up of lactic acid in the bloodstream and muscles. And it was clear that this was due to some problem in this part of the metabolism involved in converting energy from one form to another.

We had been, as I say, working on ways to identify the various proteins that are involved in this process. So when Dr. Buist consulted me, it was clear that there was the potential—based on the work we and other laboratories had been doing—for actually identifying specifically which enzymes, which proteins in this overall process might be missing and contributing to the patient's malaise. And I should say at this stage the patient, age 17, was in a wheelchair, unable to do any form of exercise.

We were able to adapt our basic scientific approaches to use on biopsy material from the patient; and for the first time ever were able to identify the level of the specific enzyme within the mitochondria and which of the particular parts of the overall apparatus involved in converting the food material into this form of energy that the muscles can use, which of the particular proteins was deficient. And, in fact, it turned out to be missing.

Fortunately, the result didn't end there with a diagnosis; because once we knew what was wrong, we were able to think about ways of improving the condition of the patient by actually bypassing this enzyme. And to cut a long story short, we were able not only to think of a regimen but to implement that regimen. And then, to make the overall research more exciting, we were able to convince a colleague of mine at the University of Philadelphia, Dr. Britton Chance, who himself is developing a very exciting new technology called whole body scan nuclear magnetic resonance, by which you can actually watch metabolism, much like we've heard earlier. But this is a slightly different type of technology.

You're able to follow metabolism in individual organs in the body. We were able to take the patient from Portland to Philadelphia, have the patient followed while we used our experimental regimen to actually monitor the change in metabolism in the muscle—one of the very first times this has happened.

We were able to see that our therapeutic regimen worked; and now this patient is no longer in a wheelchair but is actually walking in Portland. I think an important point is this is actually the first time such a diagnosis and treatment was made in a disease which happens to be much more common than perhaps was recognized because of the lack of an obvious way of diagnosis. And now the medical school and Dr. Buist is becoming a national center for the referral of patients with this disease, which is called mitochondrial myopathy. Thank you.

Senator HATFIELD. Thank you, Dr. Capaldi.

Senator DOMENICI. Great. Thank you.

Senator HATFIELD. Excellent testimony, gentlemen. We really appreciate your coming here today.

STATEMENT OF DR. VAUGHN CRITCHLOW, DIRECTOR, OREGON REGIONAL PRIMATE RESEARCH CENTER

PREPARED STATEMENT

Senator HATFIELD. Senator Domenici, we have another jewel in our great array of scientific institutions. Dr. Vaughn Critchlow is the director of the Oregon Regional Primate Research Center here in the Portland area. We're most happy to have him here today. And Dr. Critchlow, we will include your full statement in the record; and if you care to highlight it, we would appreciate hearing from you.

[The statement follows:]

Statement of Dr. Vaughn Critchlow

I am Vaughn Critchlow, Director of the Oregon Regional Primate Research Center. I am here as a science administrator and a working biomedical scientist to express my views about the importance of biomedical research to the nation's health and economy. In presenting these views, I will cite some of the research programs being carried out at our center as examples and proceed from the perspective that most of such research is federally funded through the National Institutes of Health.

Health benefits - Although small relative to the total national budget, the continuous federal investment in biomedical research since the 1950s has reaped major health benefits for our nation, benefits that are worth many times the investment. We have only to look at the classical examples afforded by the development of such things as polio and hepatitis B vaccines, oral contraceptives, cardiac and vascular surgery and organ transplants to appreciate the major improvements in health and quality of life that have resulted from the federal investment in biomedical research.

Along with these and other major advances in the understanding and treatment of important health problems have come many new conceptual and technological breakthroughs that hold great promise for even more dramatic and significant developments in the near future. The research and information bases that have been established in recent years make it reasonable to anticipate that we may soon be in a position to effectively treat or, in some cases, prevent such scourges as cancer, cardiovascular disease, genetic defects and mental disorders.

To illustrate some of the efforts our research dollars are currently supporting and the potential benefits to be realized, I would like to briefly describe a few of the research activities, all supported by peer-reviewed NIH research grants, that are ongoing at our institution.

1) Reproductive biology - The largest segment of our scientific staff is involved in reproductive biology. To many biologists and philosophers, one of the greatest threats facing our planet is over-population. Several of our scientists are working to develop the understanding and approaches essential for addressing this critical issue. For example, Dr. Nancy Alexander is making exciting progress in developing a contraceptive vaccine directed against sperm. This approach may provide a powerful new approach that can be used in men and/or women for contraceptive purposes. Dr. Dale Hoskins is investigating the biochemical mechanisms of action of gossypol, a product developed in China from cottonseed oil, the only promising new male contraceptive on the scene. Dr. Harold Spies is working on and unraveling the complex brain processes that control the reproductive system--another approach that may impact on population growth.

A unique feature of research in reproductive biology is that it is a double-edged discipline. Much of the information uncovered can be used to aid infertile couples desiring children.

Another important reproductive health problem being addressed by our scientists is premature birth; 1 of 13 babies in the U.S. are born prematurely, and these babies often have brain, lung or other serious disorders that threaten their well-being or even their lives. Dr. Miles Novy, a physician-scientist who spends 75% of his time in his basic science laboratory at the Center and 25% treating patients, uses a variety of sophisticated physiological and biochemical approaches in attempts to identify and eventually control the factors that cause premature labor.

2) Metabolic and immune diseases - Another group of our scientists is working on metabolic and immune diseases. Dr. René Malinow focuses on atherosclerosis, or hardening of the arteries, the leading cause of death in the western world. He recently found and identified substances in the alfalfa plant which reverse atherosclerosis in

monkeys. Plans are underway in collaboration with the private sector to apply these exciting findings to humans with atherosclerosis.

As a final example, I would like to cite the diabetes research of Dr. Charles Howard. Approximately 11 million Americans are diagnosed as diabetics, and another 11 million are living their lives as yet unaware that they have the disease. Although insulin and the effects of insulin deficiency were discovered many years ago, much remains unknown about diabetes, and it continues to take its annual toll. Dr. Howard works with a unique colony of monkeys which develops spontaneously a type of diabetes similar to that found in adult humans. He has made significant progress and contributions to the understanding of this form of diabetes and is currently investigating the possibility that an immune process is involved in its genesis. His concepts and theories are presently being tested in humans.

I hope that these few examples of ongoing programs at our center will illustrate the importance and potential health benefits that accrue from federal support of biomedical research.

Economic benefits - In addition to the health benefits from biomedical research, there is considerable fall-out in terms of economic impact. First and foremost, health-related research has done much and promises to do even more to reduce the staggering costs stemming from loss of employment and income because of health problems. When the amounts saved in medical and unemployment insurance and taxes are considered, the economic benefits of the investment are impressive.

In less global terms, in another dimension and closer to home, our small institution with approximately 180 employees contributes about 7 million dollars annually to the local economy. In these times and in the Portland suburbs, this is, in my opinion, a meaningful contribution to the economy of our community.

In sum, the economic benefits gained from biomedical research must surely make it one of the most cost-effective programs ever undertaken by our government.

Thank you for the opportunity to present my views on these important issues.

Biography of Dr. Vaughn Critchlow

Date and Place of Birth: March 5, 1927, Hotchkiss, Colorado

Education:

Glendale College, Glendale, California, 1946-49, A.A.
Occidental College, Los Angeles, California, 1949-51, B.A.
Occidental College, Los Angeles, California, 1951-52, Teaching Credential
University of California, Los Angeles, California, 1953-57, Ph.D.

Appointments:

Teacher, Life Science, Marshall High School, Los Angeles, California, 1952-1953

Graduate Research Anatomist, U.C.L.A., 1953-57

Instructor of Anatomy, Baylor University College of Medicine, 1957-58

Assistant Professor of Anatomy, Baylor University College of Medicine, 1958-63

Associate Professor of Anatomy, Baylor University College of Medicine, 1963-67

Professor of Anatomy, Baylor College of Medicine, 1967-72

Acting Chairman of Anatomy, Baylor College of Medicine, 1971-72

Professor and Chairman, Department of Anatomy, Oregon Health Sciences University, 1972-82

Director, Oregon Regional Primate Research Center, Beaverton, 1982-present

Research Interests:

Neuroendocrinology, endocrinology, neuroanatomy, reproductive biology

Societies

American Association of Anatomists
Endocrine Society
American Physiological Society
International Brain Research Organization
Society for Neuroscience
International Society of Neuroendocrinology

Teaching Experience:

Gross Anatomy, Neuroanatomy
Neuroendocrinology for Graduate and Medical Students
Graduate Student Training (Ph.D., M.S.)
Postdoctoral Training

Military Service:

U.S. Navy, 1945-46

Miscellaneous:

Research Career Development Award, National Institutes of Health 1959-64, 1964-69

Visiting Investigator, Nobel Institute of Neurophysiology, Karolinska Institute, Stockholm, Sweden, 1961-62

Invited Symposium Speaker:

Control of Ovulation, Harvard University, 1960

National Institutes of Health sponsored symposium on Advances in Neuroendocrinology, 1961

Second International Congress on Hormonal Steroids, Milan, 1966

Third International Congress of Endocrinology, Mexico City, 1968

U.C.L.A. Forum in Medical Sciences Conference on Steroid Hormones and Brain Function, 1970

Editorial Board of Neuroendocrinology, 1968-76

Member of the NIH Reproductive Biology Study Section, 1969-73; Ad hoc Reproductive Biology Study Section, 1975-77

Member of Scientific Advisory Committee, Oregon Regional Primate Research Center, 1973-82

Member of Ad hoc Advisory Committee, Oregon Regional Primate Research Center, 1981-82

Member of the Board of Trustees of the Medical Research Foundation of Oregon, 1982-present

Teaching Awards:

Baylor College of Medicine - 1969, 1971, 1972

University of Oregon Health Sciences Center - 1978, 1979

Current Grant Support:

NIH Research Grant RO1-AM-32442, Neural Regulation of Anterior Pituitary, 9/83-8/84, $68,378 (total project period - 9/82-8/87, Total award $380,210)

NIH Grant 2S07 RR05694, Biomedical Research Support, 4/83-3/84, $66,804

Publications

Sawyer, C. H., Critchlow, B. V., and Barraclough, C. A. Mechanism of blockade of pituitary activation by morphine, atropine and barbituates. Endocrinology 57:345-354, 1955.

Critchlow, V. Electrical correlates of neuroendocrine activity. Psychiatric Res. Reports 6:49-55, 1956.

Porter, R. W., Cavanaugh, E. B., Critchlow, B. V., and Sawyer, C. H. Localized changes in electrical activity of the hypothalamus in estrous cats following vaginal stimulation. Am. J. Physiol. 189:145-151, 1957.

Sawyer, C. H., and Critchlow, B. V. Reproduction. Ann. Rev. Physiol. 19:467-488, 1957.

Critchlow, V. Ovulation induced by hypothalamic stimulation in the anesthetized rat. Am. J. Physiol. 195:171-174, 1958.

Critchlow, V. Blockade of ovulation in the rat by mesencephalic lesions. Endocrinology 63:596-610, 1958.

Slusher, M.A., and Critchlow, V. Effect of midbrain lesions on ovulation and response to stress in female rats. Proc. Soc. Exp. Biol. Med. 101:497-499, 1959.

Elwers, M., and Critchlow, V. Precocious uterine stimulation following hypothalamic and amygdaloid lesions in rats. Am. J. Physiol. 198:381-385, 1960.

Critchlow, V. In: Control of Ovulation (C. A. Villee, ed.), Pergamon Press, pp. 75-78, 1961.

Elwers, M., and Critchlow, V. Precocious ovarian stimulation following interruption of stria terminalis. Am. J. Physiol. 201:281-284, 1961.

Critchlow, V., and von Euler, C. Rhythmic control of intercostal muscle spindles. Experientia 18:426-472, 1963.

Critchlow, V., Lipscomb, H. S., and Guillemin, R. Effect of CRF on maintenance of the adrenocorticotropic function of anterior pituitary grafts. J. Endocrinol. 25:465-472, 1963.

Critchlow, V. Role of light on the neuroendocrine system. In: Advances in Neuroendocrinology (A. V. Nalvandov, ed.), University of Illinois Press, pp. 377-402, 1963.

Critchlow, V., and von Euler, C. Intercostal muscle spindle activity and its γ-motor control. J. Physiol. 168:820-847, 1963.

Critchlow, V., Liebelt, R. A., Bar-Sela, M., Mountcastle, W., and Lipscomb, H. S. Sex difference in resting pituitary-adrenal function in the rat. Am. J. Physiol. 205:807-815, 1963.

Bradshaw, M., and Critchlow, V. Pituitary concentration of luteinizing hormone in three types of "constant estrous" rats. Endocrinology 78:1007-1014, 1966.

Bar-Sela, M., and Critchlow, V. Delayed vaginal opening following electrical stimulation of amygdala in female rats. Am. J. Physiol. 211:1103-1107, 1966.

Wagner, J. W., Erwin, W., and Critchlow, V. Androgen sterilization produced by intracerebral implants of testosterone in neonatal female rats. Endocrinology 79:1135-1142, 1966.

Lipscomb, H. W., and Critchlow, V. A study of compensatory adrenal hypertrophy. Proceedings of the 2nd International Congress on Hormonal Steroids, Milan, Excerpta Med., International Congress Series no. 111, pp. 1130-1140, 1966.

Critchlow, V., and Bar-Sela, M. Control of the onset of puberty. In: Neuroendocrinology (L. Martini and W. F. Ganong, eds.). Academic Press, New York, pp. 101-162, 1967.

Zimmermann, E., and Critchlow, V. Effects of diurnal variation in plasma corticosterone levels on adrenocortical responses to stress. Proc. Soc. Exp. Biol. Med. 125:658-663, 1967.

Zimmermann, E., and Critchlow, V. Negative feedback and pituitary-adrenal function in female rats. Am. J. Physiol. 216:148-155, 1969.

Dunn, J., and Critchlow, V. Feedback suppression of pituitary-adrenal function in rats with pituitary islands. Life Sciences 8:9-16, 1969.

Critchlow, V., and Bar-Sela, M. Central nervous system and puberty. Proceedings of the Third International Congress of Endocrinology. Excerpta Med. Int. Congr. Ser. 184:990-995, 1969.

Dunn, J., and Critchlow, V. Feedback suppression of "non-stress" pituitary-adrenal function in rats with forebrain removed. Neuroendocrinology 4:296-308, 1969.

Zimmermann, E., and Critchlow, V. Effects of intracerebral dexamethasone on pituitary-adrenal function in female rats. Am. J. Physiol. 217:392-396, 1969.

Zimmermann, E., and Critchlow, V. Suppression of pituitary-adrenal function with physiological plasma levels of corticosterone. Neuroendocrinology 5:183-192, 1969.

Dunn, J., and Critchlow, V. Pituitary-adrenal response to stress in rats with hypothalamic islands. Brain Res. 16:395-403, 1969.

Palka, Y., Liebelt, R. A., and Critchlow, V. Effects of isolation of medial basal hypothalamus on pituitary-adrenal and pituitary-ovarian functions. Neuroendocrinology 5:333-349, 1969.

Critchlow, V. Selectivity of acute feedback effects of corticosteroids on ACTH secretion. In: Steroid Hormones and Brain Function (C. H. Sawyer and R. A. Gorski, eds.). University of California Press, Los Angeles, 1971, pp. 51-58.

Dunn, J., and Critchlow, V. Vasopressin-evoked ACTH release in rats following forebrain removal. Proc. Soc. Exp. Biol. Med. 136:1284-1288, 1971.

Palka, Y., Liebelt, R. A., and Critchlow, V. Obesity and increased growth following partial or complete isolation of ventral medial hypothalamus. Physiol. Behav. 7:187-194, 1971.

Zimmermann, E., and Critchlow, V. Short latency suppression of pituitary-adrenal function with physiological plasma levels of corticosterone in the female rat. Neuroendocrinology 9:235-242, 1972.

Mitchell, J. A., Smyrl, R., Hutchins, M., Schindler, W. J., and Critchlow, V. Plasma growth hormone levels in rats with increased naso-anal length due to hypothalamic surgery. Neuroendocrinology 10:31-45, 1972.

Zimmermann, E., Smyrl, R., and Critchlow, V. Suppression of pituitary-adrenal responses to stress with physiological plasma levels of corticosterone in the female rat. Neuroendocrinology 10:246-256, 1972.

Mitchell, J. A., Hutchins, M., Schindler, W. J., and Critchlow, V. Increases in plasma growth hormone concentration and naso-anal length in rats following isolation of medial basal hypothalamus. Neuroendocrinology 12:161-173, 1973.

Dunn, J., and Critchlow, V. Pituitary-adrenal function following ablation of medial basal hypothalamus. Proc. Soc. Exp. Biol. Med. 142:749-754, 1973.

Wilson, M., and Critchow, V. Effect of fornix transection or hippocampectomy on rhythmic pituitary-adrenal function in the rat. Neuroendocrinology 13:29-40, 1973/74.

Zimmermann, E., and Critchlow, V. Inhibition of morphine-induced pituitary-adrenal activation by dexamethasone in the female rat. Proc. Soc. Exp. Biol. Med. 143:1224-1226, 1973.

Dunn, J., and Critchlow, V. Electrically stimulated ACTH release in pharmacologically blocked rats. Endocrinology 93:835-842, 1973.

Wilson, M., and Critchlow, V. Effect of septal ablation on rhythmic pituitary-adrenal function in the rat. Neuroendocrinology 14:333-334, 1974.

Fukuda, M., Greer, M. A., Roberts, L., Allen, C. F., Critchlow, V., and Wilson, M. Nycthemeral and sex-related variations in plasma thyrotropin, thyroxine, and triiodothyronine. Endocrinology 97:1424-1431, 1975.

Wilson, M., and Critchlow, V. Absence of a circadian rhythm in persisting corticosterone fluctuations following surgical isolatioin of the medial basal hypothalamus. Neuroendocrinology 19:185-192, 1975.

Rice, R. W., Kroning, J., and Critchlow, V. Effects of stress on plasma corticosterone and growth hormone levels in rats with median eminence-pituitary islands. Neuroendocrinology 19:339-351, 1975.

Rice, R. W., Kroning, J., and Critchlow, V. Sex differences in the effects of surgical isolation of the medial basal hypothalamus on linear growth and plasma growth hormone levels in the rat. Endocrinology 98:982-990, 1976.

Wilson, M., and Critchlow, V. Evidence for a free-running circadian rhythm in pituitary-adrenal function in blinded adult female rats. Neuroendocrinology 20:289-295, 1976.

Rice, R. W., and Critchlow, V. Extrahypothalamic control of stress-induced inhibition of growth hormone secretion in the rat. Endocrinology 99:970-976, 1976.

Abe, K., and Critchlow, V. Effects of corticosterone, dexamethasone and surgical isolation of the medial basal hypothalamus on rapid feedback control of stress-induced corticotropin secretion in female rats. Endocrinology 101:498-505, 1977.

Rice, R. W., Abe, K., and Critchlow, V. Abolition of plasma growth hormone response to stress and of the circadian rhythm in pituitary-adrenal function in female rats with preoptic-anterior hypothalamic lesions. Brain Res. 148:129-141, 1978.

Critchlow, V., Rice, R. W., Abe, K., and Vale, W. Somatostatin content of the median eminence in female rats with lesion-induced disruption of the inhibitory control of growth hormone secretion. Endocrinology 103:817-825, 1978.

Swan, C., Abe, K., and Critchlow, V. Effects of age of blinding on rhythmic pituitary-adrenal function in female rats. Neuroendocrinology 27:175-185, 1978.

Abe, K., Kroning, J., Greer, M., and Critchlow, V. Effects of destruction of suprachiasmatic nuclei on circadian rhythms in plasma corticosterone, body temperature, feeding and plasma thyrotropin. Neuroendocrinology 29:119-131, 1979.

Abe, K., and Critchlow, V. Delayed feedback inhibition of stress-induced activation of pituitary-adrenal function: Effects of varying dose, rate and duration of corticosterone administration and of telencephalon removal. Neuroendocrinology 31:349-354, 1980.

Critchlow, V., Abe, K., Urman, S., and Vale, W. Effects of lesions on the periventricular nucleus of the preoptic-anterior hypothalamus on growth hormone and thyrotropin secretion and brain somatostatin. Brain Res. 222:267-276, 1981.

Mioduszewski, R., and Critchlow, V. Marked and selective suppression of prolactin secretion after interruption of neural connections of the medial basal hypothalamus of the rat. Brain Res. 216:35-44, 1981.

Mioduszewski, R., and Critchlow, V. Forebrain structures which mediate the effects of stress on prolactin and growth hormone secretion in the rat. Endocrinology 110:1972-1976, 1982.

Mioduszewski, R., Zimmermann, E., and Critchlow, V. Effects of morphine dependence, withdrawal and tolerance on prolactin and growth hormone secretion in the rat. Life Sciences 30:1343-1348, 1982.

Urman, S., and Critchlow, V. Long term elevations in plasma thyrotropin, but not growth hormone concentrations associated with lesion-induced depletion of median eminence somatostatin. Endocrinology 112:659-664, 1983.

Kaler, L., and Critchlow, V. Anterior pituitary luteinizing hormone secretion during continuous perifusion in aging male rats. Mech. Ageing Dev. 25:103-115, 1984.

Kaler, L. W., Mioduszewski, R., and Critchlow, V. Anterior pituitary prolactin release in vitro after interruption of anterolateral neural connections of the mediobasal hypothalamus in male rats. Brain Res. (in press).

Dr. CRITCHLOW. Thank you, Senator Hatfield and Senator Domenici. I appreciate the chance to come and participate in these hearings.

I suppose the theme of my presentation is going to be pretty simple. Although small relative to the total national budget, the Federal investment in biomedical research since the 1950's has reaped major health benefits for our Nation, benefits that are worth many times the investment. And I would like to go on and illustrate some of the efforts our research dollars are currently supporting, and the potential benefits to be realized. I would like to briefly describe some of the research activities that are going on at our institution.

The largest segment of our scientific staff is involved in reproductive biology. One of the greatest threats facing our planet is overpopulation. Several of our scientists are working to develop the understanding and approaches essential for addressing this critical issue. For example, Dr. Nancy Alexander is making exciting progress in developing a contraceptive vaccine directed against sperm. This approach may provide a powerful new contraceptive that can be used in men or women.

Dr. Dale Hoskins is investigating the biochemical mechanisms of action of gossypol, a product developed in China from the lowly cottonseed oil. And it's the only promising new male contraceptive on the horizon.

Dr. Harold Spies and some of his colleagues are working on and unraveling the complex brain processes that control the reproductive system—another approach that may impact on population growth.

A special feature of research in reproductive biology is that it is a double-edged discipline. Much of the information uncovered is used to aid infertile couples desiring children.

Another important reproductive health problem being addressed by our scientists is premature birth. One of thirteen babies in the United States are born prematurely; and these babies often have brain, lung, or other serious disorders that threaten their well-being or even their lives.

Dr. Miles Novy is a physician-scientist who spends 75 percent of his time in his basic science laboratory at the center and 25 percent of his time treating patients. He uses a variety of sophisticated physiological and biochemical approaches in attempts to identify and eventually control the factors that cause premature labor.

Another group of our scientists is working on metabolic and immune diseases. Dr. René Malinow focuses on atherosclerosis, or hardening of the arteries, the leading cause of death in the Western World. He recently identified substances in alfalfa which reverse atherosclerosis in monkeys; and plans are underway in collaboration with the private sector to apply these exciting findings to humans with atherosclerosis.

As a final example, I would like to cite the diabetes research of Dr. Charles Howard. Approximately 11 million Americans are diagnosed as diabetics, and another 11 million are living their lives unknowing that they will be victims of the disease. Although insulin and the effects of insulin deficiency were discovered many years ago, much remains unknown about the disease, and it continues to take its annual toll. Dr. Howard works with a unique colony of monkeys which develops spontaneously a type of diabetes that is found in adult humans. He has made significant contributions to the understanding of this form of diabetes and is currently investigating the possibility that an immune process is responsible for its genesis. His concepts and theories are presently being tested in humans.

I hope that these few examples of ongoing programs at our center will illustrate the importance and potential health benefits that accrue from Federal support of biomedical research.

In addition to health benefits, there is considerable fallout in terms of economic impact. First and foremost, health-related research has done much and will do even more to reduce the staggering costs stemming from loss of employment and income resulting from health problems. When the amounts saved in medical and unemployment insurance and taxes are considered, the economic benefits of the investment will be, I am sure, impressive.

In another dimension and closer to home, our small institution with approximately 180 employees contributes about $7 million annually to the local economy. In these times and in the Portland suburbs, that is, in my opinion, a meaningful contribution to the economy of our community.

In sum, the health and economic benefits gained from biomedical research must surely make it one of the most cost-effective and people-effective programs ever undertaken by our Government. Thank you.

Senator HATFIELD. Thank you.

Senator DOMENICI. Doctor, I don't want to take a lot of time on the issue, but I understand our Federal Government's program with reference to the maintenance of the primate population of this country is a mess in terms of some conflicts on who's responsible for what. Are you aware of that problem in terms of—for instance, the hepatitis population of primates there in New Mexico is a major problem. Are you aware of that?

Dr. CRITCHLOW. No; but I wish I were.

Senator DOMENICI. A bad situation apparently.

Dr. CRITCHLOW. We're part of the national primate center system; and I hope that our activities would not be characterized as being a mess. I think there——

Senator DOMENICI. No; yours is not. What I'm talking about is that there has been some big grants into other institutions, and what's happened is they are in an argument between two or three agencies of the Government as to what to do with a very large population of primates that are sick. And they were sick because the Government experimented with them; and now they can't proceed to justify the utilization.

Dr. CRITCHLOW. I guess the only thing I know about that situation is what I've read in the paper and that's it.

Senator DOMENICI. You aren't familiar with the specifics?

Dr. CRITCHLOW. No.

Senator DOMENICI. I have no further questions.

Senator HATFIELD. Thank you very much, Dr. Critchlow. We appreciate very much your work there.

STATEMENT OF DR. DWIGHT S. "PETE" FULLERTON, PROFESSOR OF MEDICINAL CHEMISTRY, OREGON STATE UNIVERSITY

PREPARED STATEMENT

Senator HATFIELD. I would like to invite now Dr. Dwight S. "Pete" Fullerton, professor of medicinal chemistry at Oregon State University. And I might comment, Senator Domenici, that we have very strong science curriculum and leadership at Oregon State University as well as the University of Oregon. We're very happy to have you here today, Dr. Fullerton. And if you would like to submit your testimony in total and highlight it at this time, we would be very appreciative.

[The statement follows:]

STATEMENT OF DR. DWIGHT S. FULLERTON

Senator Hatfield, Senator Domenici, members of the Committee. My name is Dwight S. ("Pete") Fullerton. I am a professor of medicinal chemistry at the College of Pharmacy, Oregon State University. First and most important, I join my Oregon scientist colleagues in thanking the Committee for coming to Oregon to learn first hand about our biomedical research.

I appear before you today wearing multiple hats--as principal investigator of a national digitalis medicine study funded by the National Heart, Lung, and Blood Institute ($241,000 for the current grant year); as a scientist advisor for the NIH Division of Research Resources and for its National PROPHET Computer Resource; and as the current Faculty Senate President at OSU.

Each year, the National Institutes of Health and the National Science Foundation make reports to Congress about important health advances made possible by Federal funding. In recent years, I know the National Heart, Lung, and Blood Institute has described new advances in the treatment of coronary disease, pioneering effort as in the development of new heart valves, and exciting discoveries about the biochemical pathways which lead to blood and vascular diseases. My own comments will therefore more specifically focus on Oregon's contributions and concerns.

Biomedical Grants Are Getting Very Difficult To Obtain: The Additional $597 Million for NIH Approved By the Senate Appropriations Committee is Vital

As you know, your committee recently recommended that NIH receive enough funds to support 6,800 new and competing grants in fiscal 1985. Your efforts are much appreciated. I understand the Administration's proposed budget requested a 300 grant drop from the fiscal 1984 year level. A drop would have a most serious impact on this nation's biomedical research. The number of quality proposals already exceeds available NIH funds.

A Predictable and Stable Biomedical Funding Base is Urgently Needed

Each year Congress, NIH, NSF and the other federal biomedical funding agencies agonize about the level of biomedical research funding for the next year. This places an enormous strain on the funding agencies and on the Nation's scientific community.

Research grants are delayed; scientists are left in limbo not knowing whether to spend their time rewriting an application, or even applying at all. It is a costly, scientifically damaging situation. I offer no solution, but encourage your committee to work with NIH and NSF to discuss alternatives.

Biomedical Research at Oregon State University - The Impact of Federal Support

Oregon takes pride in contributing to the Nation's biomedical advances--at research centers in the State System of Higher Education, the Oregon Primate Center, the Oregon Graduate Center, the Mark O. Hatfield Marine Science Center, EPA laboratories, private hospitals, and private colleges.

Federal biomedical research support at Oregon State University, for example, is about $10 million dollars annually (attached table). This includes about $5.0 million from the research agencies of the Public Health Service, and about $4 million for biomedical research form the National Science Foundation. Other biomedical Federal research support is distributed among grants

from the Department of Defense, EPA, and the Department of Agriculture.

I should also point out that Oregon State University has the largest total Federal research support (for all grants, not just biomedical) of all institutions in Oregon. For the twelve months ending August 1984, we are well over $50 million in total Federal obligations. Indeed, for several years, OSU has been among the top 40 or so colleges and universities nationally for total Federal funding. We also rank 10th among all Land Grant Universities. These high rankings are all the more remarkable considering that OSU does not have its own research and teaching hospital.

What is the impact of federal funding on biomedical research at Oregon State University? The answer is simple. Without it, we would be able to do little biomedical research at all.

Where do the biomedical research funds go at OSU? My group's research is focused on the digitalis glycosides--among the ten most-prescribed drugs currently used in the United States. However, their relatively low margin of safety presents many challenges to physicians and pharmacists in treating patients. We're learning just how these drugs and their receptors work together at the molecular level. Collaborating on the study are coworkers at the University of Minnesota, and the Medical Foundation of Buffalo, New York, (A list of our current publications is attached.)

Other major biomedical research efforts at OSU include:

-A variety of projects of our Environmental Health Sciences Center (Donald Reed, Director) which are studying how environmental toxins and toxic plants affect the health of both man and livestock. Primary investigators include scientists from Agricultural Chemistry, Veterinary Medicine and Biochemistry.

-Neuropharmacology (Michael Schimerlik, Biochemistry; Lavern Weber, Director of the Mark O. Hatfield Marine Science Center; Thomas Murray, Pharmacy). Schimerlik's work, supported by the National Heart, Lung, and Blood Institute, is studying neuroreceptors critical in heart function. Murray and Weber, using both mice and fish as experimental animals, are studying the basil processes by which the brain transmits information.

-Increasing Safe Drug Utilization by the Elderly (William Simonson and Thomas Vorce-West, Pharmacy). Old people use and metabolize drugs much differently than the younger population. This NIH training project is educating health professionals about the special needs of the elderly.

-Replacing Chemicals With Biological Controls In Pest Management (George Beaudreau, Agricultural Chemistry). The toxicity of pesticides and herbicides as we all know is an increasing problem. This research, supported by both NIH and EPA, is developing safe biological control methods.

-Microbial and viral disease processes (Dennis Hruby and others, Microbiology). The focus is on the development of methods for producing new vaccine.

-Biomedical projects of the new OSU Center for Gene Research and Biotechnology (Roy Morris, Chairman) (including projects from Ken Van Holde, Henry Schaup, Chris Mathews, Gary Merrill, and others in Biochemistry; Al Ferro, Dennis Hruby, Microbiology; and my own group). The focus of the biomedical projects is largely on basic molecular biology: gene expression, structure and function of DNA and RNA, etc. My group is working on the cloning of the digitalis receptor, Na+,K+-ATPase.

-Lipid metabolism and Nutrition (Suk Oh, Nutrition Research Institute). The Institute is most concerned with learning how nutrients affect cholesterol metabolism and thus heart disease.

-Interrelationship of Human and Animal Diseases (A. Morrie Craig, Al Smith, Nancy Kerkvliet, Masaka Matsumoto, Veterinary Medicine). Bovine emphysema and related pneumonia type diseases seriously affect the health and economy of man and animals. The pathophysiology of these diseases is the focus of this research.

-Food Toxicity and Safety (Dick Scanlan, George Bailey, Joe Nixon, and others in Food Science and Technology; Margie Woodburn, Home Economics). As you know, some foods can contain toxins or carcinogens, eg nitrates and nitrites and the aflotoxins in peanut butter. These scientists are studying just how these toxins can be activated through manufacturing, cooking or by metabolism in the body--and how they actually can cause their harmful effects.

-Cancer and Oncogenes (George Bailey, Food Science and Technology; George Pearson and Ken Van Holde, Biochemistry; and many others). The work in Biochemistry is centered on oncogenes and on the roles and structure of DNA and RNA in human cancers.

-Human Nutrition (Jim Leklem, Home Economics). This research has its emphasis on Vitamin B6 and its many roles in human health.

My OSU colleagues will quickly point out a variety of other equally interesting and timely biomedical projects which should be listed. However, in my remaining time, I would like to briefly address additional topics.

Federal Biomedical Research Support's Impact on the Pharmaceutical Industry

Federally supported basic biomedical research is the foundation of the Nation's pharmaceutical industry. Examples from the perspective of a drug designer/medicinal chemist:

-Development and design of widely used organic synthesis methods by our Nation's best organic chemists (including Jim White, OSU; E.J. Corey, Harvard; H.C. Brown, Purdue; W.G. Dauben, UC Berkeley; Barry Trost, Wisconsin; to name just a few).

-The development of quantitative structure-activity drug design approaches by Corwin Hansch (Pomona College) and others. These are standard tools used by every drug design group.

-Development of Gene Splicing Techniques (P. Berg, Stanford; D. Baltimore, MIT, and others). These techniques, almost entirely developed with federal research support, have had an enormous impact on the pharmaceutical industry. New products include human insulin and human growth hormone. Merck also just announced the first genetically engineered vaccine (for hepatitis B). Other vaccine products will follow from other companies.

-Development of computer graphics to study the interaction of drugs and their receptors--by our group (especially by co-worker Douglas Rohrer at the Medical Foundation of Buffalo), Robert Langridge (UC San Francisco), Norman Allinger (Georgia), Art Olson (Scripps), and many others.

-The development of methods of drug receptor isolation and purification; the invention and development of modern biomedical research tools such as high field nmr, nmr imaging and new powerful mass spectrometers. The list could go on and on.

The message is clear. Federal biomedical research support provides the tools and knowledge which are the foundation of the Nation's pharmaceutical industry.

Rising Indirect ("Overhead") Costs

The impact of indirect costs need to be addressed to conclude the unrest this issue is causing for the biomedical scientific community, their institutions, as well as for the federal agencies - mainly NIH. A recent article in Science (20 April, 1984 - attached) addresses this problem.

Federal Biomedical Research Support is Essential for Training Biomedical Scientists

Federal biomedical research grants provide chemicals, glassware, equipment, faculty summer salaries, student stipends (including Training Grants and Fellowships), books, journals, and more. Although the Ph.D. is inherently a research degree, I am sure that Oregon is not alone in not being able to provide funds to actually do the research. Other speakers will surely address this point in greater detail.

I thank you again for your attention, and for coming to Oregon to meet with us.

OREGON STATE UNIVERSITY

Aggregate of Grants and Contracts on an Annual Basis as of February 1984 by Agencies.

Agencies	Research Grants	Equipment & Bldgs.	Institutes	Fellowships & Student Support	Training Grants	Other	Total
Environmental Protection Agency	1,061,128	---	---	---	7,230	---	1,068,358
National Aeronautics & Space Adm.	466,570	---	---	---	---	---	466,570
National Science Foundation	9,137,193	870,759	34,300	3,000	---	---	10,045,252
Office of Education	---	---	---	92,400	85,774	5,930,792	6,108,966
Office of Naval Research and Other Navy	1,145,099	173,000	---	---	---	199,626	1,517,725
Other Department of Defense	515,460	210,761	---	---	---	---	726,221
Private Foundations, Industry	8,222,958		78,800	51,990	24,000	712,670	9,090,418
Public Health Service	4,670,879	200,000	---	17,040	99,323	41,060	5,028,302
State of Oregon	1,638,025	---	---	---	---	663,263	2,301,288
U.S. Department of Agriculture	5,498,279	---	---	---	---	133,962	5,632,241
U.S. Department of Commerce	3,834,904	---	---	---	---	347,600	4,182,504
U.S. Department of Energy	1,659,962	---	---	---	---	---	1,659,962
U.S. Department of Interior	704,022	---	---	---	---	---	704,022
Other Federal Agencies	1,828,165	---	---	---	---	166,912	1,995,077
TOTAL	40,382,644	1,454,520	113,100	164,430	216,327	8,195,885	$50,526,906

GAO Report Documents Rising Indirect Costs

Though indirect costs now account for 30 percent of NIH grants, little will happen until OSTP considers the issue

A recent General Accounting Office (GAO) report* documents the sharp rise in indirect costs associated with National Institutes of Health (NIH) grants. These costs, which are paid as grant overhead to institutions to cover maintenance, administrators' salaries, and other operating expenses, have increased to about 30 percent of all NIH extramural grant expenditures. The report presents several modest proposals for getting better information about and control over what has proved to be a slippery problem—even for those determined to come to grips with it.

The impact of the GAO report might have been greater had it been completed 18 months earlier, when this issue was vigorously being raised. Instead, the report has been issued in the wake of the 1985 budget which, unlike earlier proposals, contained no provision for reducing indirect costs. Now, despite some saber rattling on Capitol Hill and the likely implementation of several of GAO's more limited proposals, the ball has been passed into the president's Office of Science and Technology Policy (OSTP), which will take a more global look at problems underlying the issue.

Undertaken at the request of Senator William Proxmire (D–Wisc.) and Senator Paula Hawkins (R–Fla.), the GAO report includes some striking figures showing how much indirect costs have been rising. During the 10-year period beginning in 1972, for example, their bite of the health research dollar grew from 21 to 30 percent, on average, and by 1982 accounted for $690 million of the $2.3 billion spent by NIH for extramural research. Proxmire cites such figures as "proof positive" that federal oversight of NIH's practices is not adequate.

NIH director James B. Wyngaarden has, however, been steadfastly seeking to restrain the rise of indirect costs, but has met consistently with stiff opposition from university administrators and from Congress (*Science*, 2 September 1983, p. 929). Last year, in order to make more money available for new and competing grants, he proposed that NIH should pay only 90 percent of indirect costs in fiscal year 1984. But the proposal was rejected by Congress, and the Administration subsequently omitted the idea from this year's budget.

The GAO report criticizes how the Department of Health and Human Services (HHS) enforces current policies. Too few audits are being conducted to determine whether indirect cost claims are valid, the report asserts. For example, the HHS Office of Audit issued only 50 indirect cost audit reports during a 5½-year period ending 30 April 1983, involving 47 of some 700 annual NIH grantees. GAO studied 40 of those audits in detail and noted that negotiators used them to disallow almost $58 million of aggregate indirect costs. Although HHS is not planning to conduct audits routinely, it will try to conduct audits when negotiators request them and plans to draw on nonfederal auditors to conduct institution-wide audits.

Another problem identified in the report is sudden jumps in an institution's indirect cost rate. Although each institution receiving an NIH grant negotiates its rate, on some occasions changes are made without adequately documented justification, the report says. HHS inspector general Richard Kusserow says that negotiators will begin documenting such matters more fully, thereby complying with one of the specific GAO recommendations.

GAO's strongest recommendation—and one that university representatives object to most strenuously—is that the Office of Management and Budget should revise current practices and establish fixed allowances for indirect costs. Those allowances might vary from one institution to the next, but they would not be allowed to fluctuate much from year to year. (Independently, several major universities, including Yale and the University of California, have agreed to fixed allowances for indirect costs. However, the idea is far from being universally accepted.)

Wyngaarden also recommends "capping" departmental and general administration costs, which are difficult to audit. However, he concedes that there may be "legitimate points being raised" by university administrators who have argued that escalating indirect costs result partly from complying with federal regulations.

Organizations representing university administrators view the final GAO report as oversimplifying this issue, and say that earlier drafts offered a fairer picture. "HHS is not doing a good job auditing," says an official from the Association of American Universities, but, "In my opinion, the conclusion [to fix indirect cost rates] does not follow from the report."

Whether university administrators can accept the proposal for a fixed cost rate or will reach some other accommodation now has become a matter for OSTP to settle. In February, HHS Secretary Margaret Heckler requested OSTP to consider the question of indirect costs. That issue will be part of a broader look at "the health of American universities," according to Bernadine Bulkley, a recently appointed deputy OSTP director. The informal plan, which is expected to take shape in the next month or two, is to thrash out "the most palatable options." There "has to be incentive within the university" to control such costs, she says. Just what those incentives might be, no one seems willing to say. Nonetheless, whatever measures are eventually deemed acceptable will need to be implemented uniformly throughout federal granting agencies, she believes.

Meanwhile, although the GAO's report will force HHS negotiators to keep better records of indirect cost rate changes, the pressure to do anything major to curb their growth is off. The scolding implicit in the report—as well as a requirement, enacted last year by Congress, that indirect costs be stipulated in NIH grant award notifications to researchers—could, however, act as a subtle curb on indirect cost growth.

—JEFFREY L. FOX

Indirect cost rates of some leading NIH grant recipients. GAO surveyed 82 of the approximately 200 institutions (from four regions) that received in 1982 more than $3 million per year in federal grant support. FY, fiscal year.

NIH grantee	FY 1982		Indirect cost as percent of total
	Total cost*	Indirect cost*	
Harvard University	55,606	22,912	41
University of Pennsylvania	52,009	18,477	36
Johns Hopkins University	51,317	16,234	32
Yale University	50,619	17,635	35
Duke University	34,351	10,823	31
University of North Carolina	26,242	6,963	26
University of Alabama in Birmingham	24,386	6,160	25
Vanderbilt University	23,328	7,868	33
Boston University	18,698	6,863	36
University of Pittsburgh	17,135	5,279	31

*Thousands of dollars. Data from GAO/HRD-84-3.

*Assuring Reasonableness of Rising Indirect Costs on NIH Research Grants—A Difficult Problem. (GAO/HRD-84-3, General Accounting Office, Washington, D.C., 1984).

Biogi aphy of Dr. Dwight S. Fullerton

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Fullerton, Dwight S.	Professor of Medicinal Chemistry	6/9/43

EDUCATION (Begin with baccalaureate or other initial professional education and include postdoctoral training)

INSTITUTION AND LOCATION	DEGREE (circle highest degree)	YEAR CONFERRED	FIELD OF STUDY
Oregon State University	B.S.	1967	Chemistry
University of California, Berkeley (W.G. Dauben)	Ph.D.	1971	Organic Chemistry
University of Virginia (S.M. Kupchan)	NIH Fellow	1972	

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. **DO NOT EXCEED TWO PAGES.**

Professional Experience:

1972-76 Assistant Professor, College of Pharmacy, University of Minnesota
1976-80 Associate Professor, School of Pharmacy, Oregon State University
1981- Professor, School of Pharmacy, Oregon State University

Public Advisory Committees:

1980-85 Biotechnology Research Resources Review Committee, DRR, NIH
1980-84 Division of Research Resources PROPHET Computer Resource Review Committee
1980-85 Oregon Heart Association Research Review Committee
1980-83 Oregon State University Research Council

National Professional Officer:

1981-82 Chairman, Medicinal Chemistry and Pharmacognosy Section, Academy of Pharmaceutical Sciences; 1980-81 Chairman-elect; 1979-80 Vice Chairman
1983-85 Chairman-elect, Chairman, Chemistry Section, American Association of Colleges of Pharmacy

Honors:

Sigma Xi
Rho Chi
"Best Teacher" Awards 1977, 1979, 1982

Memberships:

American Chemical Society
APhA, AACP, AAAS
Academy of Pharmaceutical Science

Research Support

1978-86 "Cardiac Glycoside Geometry and the Na,K-ATPase Receptor" National Heart, Lung and Blood Institute (1984-85 year, $241,000). (Principal Investigator)
1983-84 "Molecular Cloning of the cDNA Codon for the α-Subunit of Na+,K+-ATPase" Oregon State Univ. Research Council, $2250 starter grant (Principal Investigator)

Recent Publications-Fullerton Group
August 1984

D.S. Fullerton, et al, "Cardiac Glycosides 1. A Systematic Study of Digitoxin β-D-Glycosides," J. Med. Chem., 27, 256 (1984).

M. Kihara, D.S. Fullerton, et al, "Cardiac Glycosides 2. Synthesis of Glucose and Galactose Analogs," Steroids, 42, 37 (1983).

M. Kihara, D.S. Fullerton, E. Kitatsuji, et al, "Cardiac Glycosides 3. Synthesis of β-D-Digitoxose Analogs," Tetrahedron, 40, 1121 (1984).

T. Deffo, D.S. Fullerton, M.I. Schimerlik, et al, "Photoaffinity Labeling of Na+,K+-ATPase with a Cardiac Glycoside Containing the Photoactive Group on the C17 Side Chain," Biochemistry, 22, 6303 (1983).

D.C. Rohrer, D.S. Fullerton, et al, "Structures of Modified Cardenolides IV. 20,22-Dihydrodigitoxigenin Analogs," Acta Cryst. B39, 272 (1983).

K. Ahmed, D.S. Fullerton, et al, "Interaction of Na+,K+-ATPase with Digitalis Genins: A General Model for Inhibitory Activity," J. Biol. Chem. 258, 8092 (1983).

D.S. Fullerton, et al, "Use of PROPHET and MMS-X Graphics in the Study of the Cardiac Steroid Receptor Site of Na+,K+-ATPase," in Current Topics in Membranes and Transport: Structure, Mechanism and Function of the Na/K Pump (J.F. Hoffman and B. Forbush, eds) Academic Press, 19, 257 (1983).

B. Simat, K. Ahmed, D.S. Fullerton, et al, "Is the Erythrocyte Sodium Pump Altered in Human Obesity?" J. Clin. Endrocinology and Metabolism, 56, 925 (1983).

A.H.L. From, D.S. Fullerton, et al, "The Inotropic Activity of Digitalis Genins is Dependent Upon C17 Side Group Position," J. Mol.and Cellular Cardiology, in press.

D.C. Rohrer, D.S. Fullerton, et al, "Cardiac Glycosides 4," J. Amer. Chem. Soc., submitted.

D.C. Rohrer, D.S. Fullerton, et al, "Structures of Modified Cardenolides V," Acta Cryst, submitted.

D.S. Fullerton, H. Rathore, K. Igarishi, et al, "Cardiac Glycosides 5," J. Org. Chem., submitted.

G. Peterson, D.S. Fullerton, M. Yamaki, M.I. Schimerlik, "Purification of the Muscarinic Receptor," Proc. Nat. Acad. Sci., USA, in press.

D.S. Fullerton, et al, "Modeling the Cardenolide Receptor," in Topics in Molecular Pharmacology (Roberts and Burgen, Eds), Elsevier, in final preparation.

J. Griffin, D.S. Fullerton, T. Hashimoto, et al, "Gitoxigenin Analogues 1," J. Med. Chem., submitted.

Dr. FULLERTON. Thank you very much. First of all on behalf of all the scientists here and the other scientists from Oregon who could not be here, I can't tell you how pleased we are that you've both made the trip to Oregon. And we're especially pleased to have learned midsummer about the fine work of both of your committees and the increase in the appropriation to NIH. It was great news and we appreciate it.

There is an advantage in being toward the afternoon in a series of speakers. It gives me the opportunity to address and focus on highlights which perhaps others had not covered indepth, and to tell you about some things that they haven't told you about. So I'm going to address, really, four issues, three of which impact on the Nation and the benefit of biomedical research on the Nation. And the last, fourth out of the four, the impact of biomedical research support at Oregon State University.

I'm here today wearing multiple hats, as most of the scientists giving testimony here today were also; first as a medicinal chemist and molecular pharmacologist. I guess some would call me a drug designer. Second, as the principal investigator for a major national study of digitalis medicines supported by the National Heart, Lung, and Blood Institute. Third, as others in the room, as a scientist adviser for NIH and others for NSF. And fourth, as the current faculty representative, faculty senate president at Oregon State University.

Now for the four points I was going to make. If you will permit me, you've given me the opportunity to summarize the points I made in my prepared testimony, to go a little out of order, to address some points which have not yet been fully covered.

First again, is to thank you for your support. The number that we heard about in Oregon was a $579 million increase for NIH in biomedical research. The number now appears to be even over $650 million. That's great news and will have an enormous impact.

Chairman Domenici asked two of the previous witnesses about the impact of biomedical research on our young scientists. And certainly one of the big turnoffs now for young scientists pursuing research in careers in academia and in research institutes is the severe competitive nature of getting NIH support.

In the pharmaceutical sciences that I know most about, some of our best people—and, in fact, many of our best graduate students—are going to industry. And we're not having the benefit of their training and their knowledge in the pursuit of basic knowledge. So we applaud you; it's good news.

We especially applaud you because the Nation really needs a stable and predictable funding base. I think everyone in the room has been caught between Federal appropriations to NIH or NSF. While NIH and NSF are working on continuing resolutions, and there will be a period of 2 or 3 months where you don't know if you're going to be funded or not, the agency can't either encourage you or discourage you. You're not sure if you should resubmit or apply at all.

So if there is a way to achieve some stability, it would be great. I don't really have a good model; don't really have a good suggestion. NASA, I understand, has a relatively long-term funding basis, and perhaps NASA can be a model. But it is certainly scientifically disrupting, perhaps even damaging, to have this overlap of many scientists being uncertain if they can do their work or not. And it happens every year and it happens to a lot of scientists. That's the first point.

A point that has been made but not fully addressed earlier this afternoon is the impact of Federal biomedical research—supported research—on the pharmaceutical industry, an industry that is, of course, very close to the college of pharmacy.

It's not an exaggeration to say unequivocally that Federal support, Federal research—supported biomedical research—is the foundation of this Nation's pharmaceutical industry. It's the foundation.

Let me give you some examples. One example is in the area of synthetic organic chemistry. Organic chemical reactions are the tools by which the Nation's drug companies and their chemists make new drug molecules. Where do those methods come from? They come from Jim White of Oregon State University, Virgil Beckelhyde of the University of Oregon, E.J. Corey of Harvard, Barry Trost of Wisconsin, and others all supported by Federal funds.

Another example, much has been spoken this afternoon of the advances in molecular biology. A comment that I think has not been made yet is that the advances in gene splicing techniques—and I should say the development of the gene splicing techniques—was almost entirely done with the help of Federal support, and almost exclusively with Federal support.

But then industry builds on those and applies them to the development of new products. Two have been mentioned already this afternoon, a third has not. The two that have been mentioned are human insulin, which is now being produced as a result of gene splicing techniques, and human growth hormone. The one that has not been mentioned is a new product of Merck, which was just announced last month. It's the first vaccine for hepatitis. And you were mentioning before, Senator Domenici, about hepatitis. This is an enormous breakthrough and will not be the last of what I predict to be a continuing series of new vaccines, all made possible by Federal supported research at the academic and research institute level.

Senator DOMENICI. Is there any impediment from the research you describe going to the private sector of pharmaceutical utilization?

Dr. FULLERTON. Not at all; not at all. In the case of synthetic organic chemistry, it's published. Their chemists pick it up. In the case of gene splicing techniques, the same is true. Those fundamental tools—the carpenter's hammer and saw, if you will—are used by the drug designers and drug developers in the industry. So it's a fundamental part, I think, of this Nation's economy, as reflected in a very vigorous and, I think, very productive pharmaceutical industry.

Another example: The whole area of computer graphics in drug design. I attended a scientific conference in drug design this summer at SUNY Buffalo in New York, the State University of New York. And scientists in industry have now taken some of the tools that Federal support made possible in looking at drug receptors on computers and measuring precise little crevices to design new drugs.

The most exciting of all, I think, right now are antisickling drugs to prevent and cure sickle cell anemia—a dramatic breakthrough but I suspect the product won't be out on the market for several years. But they have done it; the drug has activity. It's really exciting.

Other examples can be made. The development of quantitative structure activity relationship based drug design. That's a mouthful, but it's an inherent part of the approach used by virtually every drug design group in industry. And it was all based at Pomona College in California in one of the colleges just outside Los Angeles, all with Federal funds.

Well, the list could go on and on. The development of tools to isolate drug receptors; the development of high field NMR and NMR imaging; the development—since I have been serving with a division of research resources—a development of these other powerful tools used by everyone doing fundamental and applied biomedical research would not have been possible without Federal funding. That's the second point.

The third point which has not been addressed except indirectly is the importance of Federal biomedical research support on the training of our scientists—and you addressed it briefly, Chairman Domenici. I would like to build on it.

The Ph.D., is, of course, we all know, inherently a research degree. But Oregon is not alone in not being able to afford the funds to provide the research tools and the research capacity for modern biomedical training for these new Ph.D.'s. We're virtually dependent upon Federal funds to permit high-quality biomedical scientists, Ph.D.'s being trained. So it's an absolute life blood of every Ph.D. program that I know about in this Nation.

The first three points have been on biomedical research and how it affects the Nation. Let me tell you a little bit how it affects Oregon State University.

Oregon State University is a diverse university encompassing many of the so-called high tech areas, as well as agriculture, a very strong center for marine science and oceanography, and a variety of other areas. How does biotechnology research support affect Oregon State University?

Well, our total biomedical research support at the present time is about $10 million; about $5 million from NIH, and about $4.5 million from NSF, with an additional several hundred thousand dollars from DOD, Department of Agriculture, on biomedical-related projects, et cetera. And I have to take this opportunity in pride to point out that Oregon State University's total Federal research funding, both biomedical and nonbiomedical, is as of this month over $50 million annually, which makes us and has made us over the last several years among the top 40 or so universities and colleges nationally for Federal obligations. It's a credit to some exciting science that goes on in Corvallis.

We rank among the top 10 for land grant universities in overall research support by the Federal Government.

What's the impact of those dollars on Oregon State University? One I mentioned, of course, already, without those funds we would not have viable Ph.D. programs.

The second thing is without those funds we wouldn't be able to do much research because research is expensive and it takes equipment. It takes glassware and it takes chemicals, all of which is beyond, as I mentioned before, the capacity of most States to provide.

Where do those funds go at Oregon State University? Let me give you a few examples, first with my own group's research.

There's a tall, lovely flower that Senator Hatfield knows a lot about because it grows all over western Oregon in the spring. It's digitalis, a tall flower about so big [indicating]. I'm sure you both have seen it. It's also, in addition to being a pretty flower, the source of digitalis glycosides which are among the top 10 most prescribed drugs in the United States.

They're absolutely miracle drugs but they have a problem, and the problem is that the margin of safety between their effective dose and their toxic dose is rather narrow. They are used both for congestive heart failure, and they're used for a variety of heart arrhythmias.

What we're trying to do in this project, which is centered in Oregon—also in Minnesota and New York—is to learn how they work at the molecular level. And we're using computer graphics, and we're using drug design, and we're using biochemistry to sort all that out.

Another project that's a very important one at Oregon State University is environmental health sciences. And we have a group of investigators who are very concerned about the presence of toxins in the environment and how we can minimize their effect. And also the toxins which naturally appear in some plants and how they affect livestock.

Neuropharmacology is a major area of research at Oregon State University. The director of the Mark O. Hatfield Marine Science Center, Lavern Weber, is probably our leading investigator in this area; but also Mike Schimerlik in biochemistry, supported by the National Heart, Lung, and Blood Institute; and Tom Murray in pharmacy are doing work both on the heart and on the brain and learning about nerve function.

Other research has to do with lipid metabolism and nutrition, learning how nutrients in the body can affect cholesteral biosynthesis and production and thus heart disease. George Beaudreau in agricultural chemistry has a major project learning how biological controls can take the place of toxic chemicals in the control of pests and as herbicides as well.

A project that is an important one in the college of pharmacy is learning how and training health professionals how to use drugs appropriately for the elderly. I think as you know, as you get older we tend to absorb drugs differently than we did when we were 21, and we tend to metabolize drugs differently. And this training project from NIH has

focused on training health professionals to learn about those unique characteristics of the elderly and to prescribe appropriately.

I could go on and on and on with diseases that affect both man and animals. We're concerned with food toxicity, nitrates, and nitrosoamines. Much of the fundamental work in the area was done at Oregon State University, two investigators working with oncogenes. The list goes on. We take a great deal of pride in our research. But the bottom line is without your help it wouldn't happen.

So with that, thank you again. It's been a pleasure to be here.

Senator HATFIELD. Thank you, Dr. Fullerton, for your very impressive testimony Senator Domenici, do you have any questions?

Senator DOMENICI. Just one. It would seem to me that what we've been hearing about in terms of basic research and targeted research that there certainly is room for maximizing in a scientific manner the availability of information in the general scientific investigative arena with those doing targeted research. It also seems to me that that would have been more difficult 25 years ago than now—should be. Of course we have some rather magnificant ways to communicate now.

Dr. FULLERTON. Absolutely.

Senator DOMENICI. Is something being done about matching that up better?

Dr. FULLERTON. It's being matched up actually reasonably well today through the support that both your committees give to the National Library of Medicine, and the computer data retrieval systems that relatively easily bring data that we used to have to dig through chemical abstracts and biological abstracts and other abstracts to find, really in a matter of minutes, at your fingertips.

The developments of the National Library of Medicine in computerizing basic medical information is really revolutionary and is making all of everyone's job easier, whether it's in applied research or basic research. So it's an important area, and you're right. And I think some exciting things are happening and will continue to happen.

Senator DOMENICI. You know, Senator Hatfield, that new insulin pump that we're going to be using nationally—am I talking about something that you all know about? That was an accidental match-up. The medical school was doing one piece of research and a great big nuclear lab that's doing science research for nuclear bomb safety happened to be having their best scientists talk together in symposia. And the physics was in the science lab and the medicine was in the medical researchers; and in about 8 months they found out that they could marry them up and that's where they got the physics. That just came to mind as you talked about the basic research versus the drug. It seems to me that as much emphasis as possible ought to be put into matching up the general research with the targeted research. And I assume that must be happening.

Dr. FULLERTON. Sure, it is. There are some important practical drives that I think even in the so-called basic research makes many basic research grant applications look fairly applied. Part of grantsmanship, as

we all in the audience will attest to, is in making your basic research—arguing for the practically of your basic research.

If your research is super high risk, it has to have enormous scientific merit to be funded. If it's super high risk but has a very targeted goal that seems in the view of the reviewing panel to have its shot, it's got a very high chance for success. So even the people that I mentioned before as organic chemists designing new reactions, shape their grant proposals around biologically active molecules, the modification of which have a good chance for being useful drugs.

Senator DOMENICI. Thank you, Mr. Chairman.

Senator HATFIELD. Thank you, Dr. Fullerton. Thank you, Senator Domenici.

We have, at this point, heard primarily from the academic institutions as they relate to reseach and the primate center. And now I would like to shift gears a moment and invite a panel from the setting of medical research, in a community hospital framework.

STATEMENTS OF:

DR. NEAL H. BARMACK, CHAIRMAN, GOOD SAMARITAN HOSPITAL AND MEDICAL CENTER, NEUROLOGICAL SCIENCES INSTITUTE

DR. F. OWEN BLACK, DIRECTOR OF VESTIBULAR CLINIC, GOOD SAMARITAN HOSPITAL AND MEDICAL CENTER, NEUROLOGICAL SCIENCES INSTITUTE

DR. LILLIAN M. PUBOLS, SENIOR SCIENTIST, GOOD SAMARITAN HOSPITAL AND MEDICAL CENTER, NEUROLOGICAL SCIENCES INSTITUTE

Senator HATFIELD. Senator Domenici, we have a number of outstanding community hospitals in Portland, and one today that we will be hearing from is the Good Samaritan Hospital and Medical Center for Neurological Sciences Institute.

It was my privilege recently to help top off some new construction in which they will be housing their basic science research institute. This is an investment of primarily private dollars and contributions. It's a great pleasure to welcome to our hearing, Dr. Neal Barmack, who is chairman; and Dr. F. Owen Black, who is director of the vestibular clinic; and Dr. Lillian Pubols, senior scientist, to come forward and take a chair and present to us the final testimony today of our hearing.

PREPARED STATEMENT

Please proceed in the order in which you wish to summarize your testimony or engage in interchange or however you wish to present it. We're happy to welcome you here.

[The statement follows:]

STATEMENT OF DR. NEAL H. BARMACK

Senator Domenici, Dr. Goldstein, Mr. Chairman, and other members of the Senate Appropriations Committee, my name is Neal Barmack and I am the Chairman of the Neurological Sciences Institute of Good Samaritan Hospital and Medical Center, with me today are Dr. Owen Black, Dr. Alvin Eisner, Dr. Gin McCollum, Dr. Lillian Pubols, and Dr. Benjamin Pubols. I am a member of the Visual Sciences Study Section of the National Eye Institute and a member of the Editorial Board of Vision Research, a scientific publication devoted to the experimental analysis of vision. I am a member of the Program Committee of the Neuroscience Society which has an active membership of 5,000 neuroscientists united by a common interest in determining how the nervous system works. I received my doctoral degree in neurobiology from the Center for Brain Research at the University of Rochester in 1970.

In the fall of 1970, I accepted a position as a full-time research scientist in the laboratory of neurophysiology then headed by Dr. Robert Dow, an eminent neuroanatomist and neurologist. Since that time the laboratory has changed its name to the Neurological Sciences Institute and the staff of the laboratory has tripled to its presently constituted size of 16 scientists.

How did the Neurological Sciences Institute find a home and sponsor at the Good Samaritan Hospital and Medical Center? In the early 1970's, Good Samaritan Hospital and Medical Center was already noted for its high quality of medical service. The Administration of the hospital recognized that in order to maintain its preeminence as a provider of tertiary care particularly in the areas of neurology and ophthalmology, it would be necessary to establish a broadly based basic biological research program. This broadly based basic research program was established with four expectations: 1) An active research program could attract outstanding clinicians who in turn would enhance the standards of general medical practice in the community. 2) A research program

could provide a valuable educational resource for the training of future medical practitioners; interns, residents, special fellows. 3) Since biological research requires a broad range of technical skills, a nucleus of basic scientists could provide a resource of technical knowledge for the rapidly evolving technical changes in the practice of medicine. 4) A broadly based research program might suggest new methods of diagnosing and treating disease.

The fulfillment of these objectives was expected to be a logical outcome of recruiting a talented scientific staff with basic research interests in how the brain works and giving them total freedom of inquiry to pursue their own self-directed research programs. This last point is very important because people unfamiliar with the complexities of biomedical research and the relationship between laboratory findings and improvement in health care frequently conceive of research as a targeted effort similar to the NASA program which enabled the United States to achieve preeminence in space. While the NASA program was successful, its success was one of engineering and logistical planning rather than of discovering fundamental astrophysical or geophysical laws. However, most diseases are incompletely understood and therefore the NASA analogy for targeted research is inappropriate. Therefore, the NSI was established with the belief that self-directed basic research, although less predictable in outcome, would nevertheless provide practical benefit to the Good Samaritan Hospital and Medical Center as well as a better fundamental understanding of the areas in which this research was conducted.

Individual scientists were recruited to Good Samaritan Hospital and Medical Center by providing them with appointments to the Neurological Sciences Institute and a joint appointment to an appropriate clinical department. For example, since my own research is directed toward understanding the laws which govern the control of eye movements, I have a joint appointment at the Neurological Sciences Institute and the Department of Ophthalmology. Other scientists have appointments in the

Departments of Neuro-otology, Neurology, Neurosurgery, and Physical Medicine and Rehabilitation. This organization differs from most conventional academic environments in which basic research scientists are frequently isolated from their clinical colleagues.

There is a vast array of separate research projects currently being undertaken at the Neurological Sciences Institute -- frequently with clinical implications. A few illustrative examples will emphasize this point.

1) Under the direction of Dr. William Roberts, a member of the Department of Neurosurgery, experiments are in progress which seek to understand the role of the autonomic nervous system in the control of pain. Already the research of Dr. Roberts has spawned new procedures which have been implemented in the establishment of a pain clinic at Good Samaritan Hospital and Medical Center.

2) Under the direction of Dr. Lewis Nashner, a member of the Department of Neuro-otology, experiments have been going on for over a decade exploring how different sensory inputs contribute to our ability to maintain balance. The success of these experiments has produced new diagnostic techniques which are currently being implemented in the laboratory of Dr. Owen Black, recruited to head the Department of Neuro-otology, who was attracted to Good Samaritan Hospital and Medical Center primarily by Dr. Nashner's research program. The technical advances achieved by this joint collaboration provide a significant improvement in the diagnosis of vestibular disorders in humans. This means that less exploratory surgery will be necessary for many patients suffering from vestibular disorders. This, of course, will reduce the cost of medical treatment.

A private company has been formed by Dr. Nashner and financed with the aid of a Small Business Initiative Grant from the National Institutes of Health to develop a marketable apparatus which could be used in other departments of neuro-otology throughout the world.

3) Research conducted in the laboratory of Dr. Paul Cordo, a member of the Department of Physical Medicine and Rehabilitation, seeks to understand the laws governing the control of arm movements. These experiments have practical implications for the application of robotic principles to the control of prosthetic limbs in amputees and for the possible improved treatment of paraplegics.

4) Research in the laboratory of Dr. Michael Kaplan, a member of the Department of Ophthalmology, seeks to understand the laws which govern the growth and aging of the photoreceptors of the eye. These experiments have implications for understanding the disease process underlying retinitis pigmentosa.

5) Research in my own laboratory on the effect of certain drugs on the vestibular system, the system which controls the sensation of body movement, has direct implications for motion sickness, space exploration, and for the action of tranquilizers.

6) Experiments conducted by Dr. Alvin Eisner, a member of the Department of Ophthalmology, on the effect of age on the perception of light and color offer great promise for understanding the fundamental mechanisms which underly our ability to adapt to different levels of visual illumination. At the same time these experiments offer the possibility of achieving an early diagnosis of certain retinal diseases.

7) Two members of the NSI, Dr. Don Rushmer of the Neurology Department and Dr. Lee Robertson of the Neurosurgery Department are conducting experiments designed to understand how the brain translates simple commands into postural adjustments.

8) Dr. Gin McCollum, a member of the department of Neuro-otology, is attempting to formulate a new quasi-mathematical vocabulary for describing how movements in normal human subjects and patients with sensory disorders are regulated.

9) Dr. Curtis Bell, a member of the department of Neurology, is studying how the brain formulates commands to generate movement and how these commands influence sensory information during movement.

40-856 O - 85 -- 9

10) Under the direction of Dr. Lillian Pubols, a member of the Department of Neurosurgery, investigations are underway which seek to characterize at a cellular level mechanisms behind spinal cord regeneration. This research has obvious implications for people suffering from spinal impairment caused by trauma, such as patients seen at the Rehabilitation Institute of Oregon.

These are just some of the examples of research being conducted at the Neurological Sciences Institute. There are many more projects being undertaken with equal scientific promise and a sense of genuine excitement. If you were to visit the Neurological Sciences Institute, you would see that each of these briefly described experiments has a unique instrumentation associated with it. Depending on the level of the scientific questions posed by these investigations different experimental subjects are required. Human subjects are used in many of the projects, but many basic questions require the use of animals.

How has this research fulfilled the goals of the Good Samaritan Hospital and Medical Center? 1) Outstanding clinical chiefs have been recruited in a number of different areas including ophthalmology, neuro-otology, epilepsy, and neurology, making Good Samaritan Hospital and Medical Center the regional referring hospital for diseases of the eye and central nervous system. 2) Scores of interns, residents, postdoctoral fellows, special fellows, undergraduate students from local colleges, and graduate students from local universities have received training in the neurosciences at the Neurological Sciences Institute. 3) Good Samaritan Hospital and Medical Center has been a leader in the development of new diagnostic techniques using the base of knowledge at the Neurological Sciences Institute as a springboard. For example, the first electronic technician at the Neurological Sciences Institute, Mr. Lawrence Mills, was largely responsible for the implementation of all the new diagnostic techniques used for cardiovascular physiology and surgery. A student from my laboratory, Mr. Dan Lulich, was hired by the Department of Ophthalmology to instrument sophisticated

electrophysiological, computer-based tests for diagnosing multiple sclerosis and retinitis pigmentosa. 4) New technical procedures which enhance medical knowledge and lead to improved medical diagnosis have been developed by members of the Neurological Sciences Institute in collaboration with appropriate clinical departments. In a very real sense, all the objectives of the Good Samaritan Hospital and Medical Center in establishing the Neurological Sciences Institute have been and will continue to be achieved. In a practical sense this means that Oregonians will receive improved medical treatment.

How is the Neurological Sciences Institute funded? Primarily by individual research grants competitively obtained through the peer review system of the National Institutes of Health. Over 85% of our $1,200,000 annual budget comes from such research grants. Some of our work is sponsored by other agencies such as the National Science Foundation and the National Aeronautics and Space Administration. Some of our research is sponsored by the Oregon Lions Sight and Hearing Foundation. In addition to providing more than 1.5 million dollars to construct a new Devers Eye Clinic in the new Neurological Sciences Center building, visited by Senator Hatfield just this last week, the Oregon Lions Sight and Hearing Foundation earmarks a percentage of its annual budget to support basic research as well as patient care.

Scientific grantsmanship is an extremely competitive enterprise. Individual grant proposals made to different divisions of the National Institutes of Health have on the average less than one out of three chance of being funded. In spite of these odds, every member of the Neurological Sciences Institute is currently funded. Included in the funding record is the work of Dr. Benjamin Pubols who last month became Oregon's first Javits Investigator, a winner of a highly coveted research award worth over one million dollars and lasting seven years.

The continued success of the Neurological Sciences Institute depends on four factors: 1) Our ability to do outstanding scientific

research. 2) Our ability to serve as an educational and technical resource to Good Samaritan Hospital and Medical Center. 3) The availability of federal funding based on a peer-review merit system. 4) Continued development of affiliations with private and public institutions interested in biomedical research and its practical application to man.

My colleagues at the Neurological Sciences Institute and I appreciate the important leadership which Senators Hatfield and Domenici have exercised in making the case for continued and enhanced federal support for this research. Our laboratories and clinics will always be open for your inspection and our scientific staff stands ready to assist you in this enterprise. Thank you for your attention.

NEUROLOGICAL SCIENCES INSTITUTE, GOOD SAMARITAN HOSPITAL

Neal H. Barmack, Ph.D., Senior Scientist, Neurological Sciences Institute

Doctorate in Neurobiology (1970) from the University of Rochester
Postdoctoral in Neurophysiology (1971) University of Oslo
U.S. Public Health Service predoctoral trainee, Center for Brain Research
U.S.P.H.S. postdoctoral fellow, Oslo
1970 Dept. of Ophthalmology (Devers Eye Clinic) Good Samaritan Hospital
1975 Neurological Sciences Institute, Good Samaritan Hospital
Member, Visual Sciences Study Section B, National Institutes of Health
Editorial Board, Vision Research

Research: The relationship between head and eye movements and their importance to the sense of balance.

F. Owen Black, M.D., Chief of Neuro-otology; Senior Scientist, Neurological Sciences Institute

M.D. (1963) University of Missouri
Residencies: Albuquerque, N.M.; Denver, Col. (U. of Colorado)
1968 University of Colorado Medical Center faculty
1971 University of Florida College of Medicine (Gainewville) faculty
1974 University of Pittsburgh Eye and Ear Hospital faculty
1982 Good Samaritan Hospital & Medical Center
National Foundation Scholar (1959-63)
NIH Special Research Fellowship (1968-69)
NIH Research Career Development Award (1972-77)
President, Asso. for Research in Otolaryngology
Advisory Cte., National Research Council Cte. on Hearing, Bioacoustics & Biomechanics
Chairman, Advisory Committee, Space Biomedical Research Inst., University Space Research Asso. (1982-)

Research: The cause and treatment of dizziness and balance problems.

Biography of Dr. Neal H. Barmack

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Neal H. Barmack	Associate Professor of Biological Sciences	8-23-42

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Michigan (1960-1964)	B.S.	1963	Psychology
University of Rochester (1964-1969)	Ph.D.	1970	Neurobiology
University of Oslo (1969-1970)	Postdoctoral	--	Neurophysiology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

1963-1964 Research Assistant with Dr. C. M. Butter, University of Michigan
1964-1968 U.S.P.H.S. Predoctoral Trainee, Center for Brain Research
1968-1969 Departmental Fellow, University of Rochester
1968-1969 Assistant Lecturer, University of Rochester
1969-1970 U.S.P.H.S. Postdoctroal Fellow with Dr. Per Andersen, Institute of Neurophysiology, University of Oslo, Norway
1970-1972 Research Associate, Laboratory of Neurophysiology, Department of Opthalmology, Good Samaritan Hospital and Medical Center
1972 Neurosciences Research Program Fellow for Third Intensive Study Program
1972-1975 Senior Research Associate, Laboratory of Neurophysiology, Department of Opthalmology, Good Samaritan Hospital and Medical Center
1975-1980 Associate Scientist, Department of Opthalmology, Neurological Sciences Institute, Good Samaritan Hospital and Medical Center
1980-1981 Senior Scientist, Department of Opthalmology, Neurological Sciences Institute, Good Samaritan Hospital and Medical Center
1981-1985 Member, Visual Sciences Study Section B, National Institute of Health
1981- Associate Professor of Biological Sciences, The University of Connecticut, Physiology Section, Storrs, Connecticut
1982 Member, Editorial Board of Vision Research

PUBLICATIONS

Barmack, N. H. 1977. Visually-evoked activity of neurons in the dorsal cap of the inferior olive and its relationship to the control of eye movements. In: Control of Gaze by Brainstem Interneurons. R. Baker and A. Berthoz (eds.) Pergamon Press: London. 361-370.

Barmack, N.H., Henkel, C.K. and Pettorossi, V.E. 1979. A subparafascicular projection to the medial vestibular nucleus of the rabbit. Brain Research 172:339-343.

Barmack, N.H. 1980. Immediate and sustained influences of visual olivocerebellar activity on eye movement. In: Control of Posture and Movement: Perspective for Integrating Sensory and Motor Research on the Mammalian Nervous System. R.E. Talbott and D.R. Humphrey (eds.) Ravin Press: New York. 123-168.

Barmack, N.H. and Hess, D.T. 1980. Multiple unit activity evoked in the dorsal cap of the inferior olive of the rabbit by visual stimulation. J. Neurophysiol. 43:151-164.

Barmack, N.H. and Hess, D.T. 1980. Eye movements evoked by microstimulation of the dorsal cap of the inferior olive in the rabbit. J. Neurophysiol. 43:165-181.

Barmack, N.H. and Simpson, J.I. 1980. The effects of microlesions of the dorsal cap of the inferior olive of rabbits on optokinetic and vestibuloocular eye movements. J. Neurophysiol. 43:182-206.

Barmack, N.H. and Pettorossi, V.E. 1980. Vestibuloocular reflexes in rabbits: Reduction by intravenous injections of diazepam. Arch. Neurol. 37:718-722.

Barmack, N.H. and Pettorossi, V.E. 1980. The influence of diazepam on the activity of secondary vestibular neurons in the rabbit. Neuroscience Letters 16:339-344.

Barmack, N.H. and Pettorossi, V.E. 1980. Influence of a GABA agonist, diazepam, on the vestibuloocular reflexes of the rabbit. Brain Res. Bull. 5, Suppl. 2:705-712.

Barmack, N.H., Pettorossi, V.E., and Erickson, R.G. 1980. The influence of bilateral labyrinthectomy on horizontal and vertical optokinetic reflexes in the rabbit. Brain Res. 196:520-524.

Erickson, R.G. and Barmack, N.H. 1980. A comparison of horizontal and vertical optokinetic reflexes in the rabbit. Exp. Brain Res. 40:448-456.

Barmack, N.H. 1981. A comparison of the horizontal and vertical vestibuloocular reflexes of the rabbit. J. Physiol. 314:547-564.

Barmack, N.H., Pettorossi, V.E., and Nastos, M.A. 1981. The horizontal and vertical cervicoocular reflexes of the rabbit. Brain Res. 224:261-278.

Barmack, N.H. and Pettorossi, V.E. 1981. Influence of olivo-cerebellar inactivation on the optokinetic sensitivity of secondary vestibular neurons. In: Progress in Oculomotor Research. Fuchs, A.F. and Becker, W. (eds.) Elsevier North Holland: Amsterdam. 455-464.

Barmack, N.H. and Pettorossi, V.E. 1981. The influence of unilateral horizontal semicircular canal plugs on the horizontal vestibuloocular reflex of the rabbit. In: Lesion-induced Neuronal Plasticity in Sensorimotor Systems. Flohr, H. and Precht, W. (eds.) Springer-Verlag: Berlin. 231-239.

Barmack, N.H. and Pettorossi, V.E. The effects of plugs of the semicircular canals on vestibuloocular reflexes in the rabbit. J. Physiol. (Submitted.)

Barmack, N.H. and Pettorossi, V.E. 1982. A comparison of horizontal and vertical vestibuloocular reflexes and the influence of selective semicircular canal plugs upon them in the rabbit. In: Vestibular Function and Morphology. Gualtierotti, T. (ed.) Springer-Verlag, ~~(in press).~~

Barmack, N.H., Henkel, C.K., and Pettorossi, V.E. 1982. Central projections to the vestibular nuclei from the subparafascicular region of the rabbit. In: Vestibular Function and Morphology. Gualtierotti, T. (ed.) Springer-Verlag, ~~(in press), 1982.~~

Barmack, N.H. 1982. Extraocular muscle stiffness in normal rabbits, cats and visually deprived cats. In: Functional Basis of Ocular Motility Disorders. Lennerstrand, G., Scott, A. and Keller, E. (eds.) Pergamon Press: Oxford.

Barmack, N.H. and Pettorossi, V.E. The effects of unilateral lesions of the flocculus on optokinetic and vestibuloocular reflexes of the rabbit. J. Physiol. (submitted).

Barmack, N.H. 1982. The influence of bilateral labyrinthectomies and bilateral plugs of the semicircular canals upon vestibuloocular and optokinetic reflexes of the rabbit. In: Physiological and Pathological Aspects of Eye Movements. Roucoux, A. (ed.) Elsevier North Holland.

Biography of Dr. Lillian M. Pubols

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Lillian M. Pubols	Senior Scientist	October 13, 1939

EDUCATION (*Begin with baccalaureate training and include postdoctoral*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Douglass College, New Brunswick, N.J.	A.B.	1961	Psychology
University of Wisconsin, Madison, WI	M.A.	1964	Physiological Psycholo
University of Wisconsin, Madison, WI	Ph.D.	1966	Physiological Psycholo

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

PREVIOUS EMPLOYMENT

1966 - Research Assistant, Animal Behavior Research Laboratory, The Pennsylvania State University, University Park, PA.

1966-1967 - Research Associate, Animal Behavior Research Laboratory, The Pennsylvania State University, University Park, PA.

1967-1971 - Research Associate, Department of Anatomy, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA.

1971-1974 - Assistant Professor of Anatomy, Department of Anatomy, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA.

1972-Summer - Visiting Senior Research Fellow, Somatosensory Research Group, Department of Veterinary Physiology with Dr. A. Iggo, Royal (Dick) School of Veterinary Studies, The University of Edinburgh, Edinburgh, Scotland, June-September.

1974-1977 - Assistant Professor of Anatomy, Department of Anatomy, The Medical College of Pennsylvania, Philadelphia, PA.

1977-1982 - Associate Professor of Anatomy, Department of Anatomy, The Medical College of Pennsylvania, Philadelphia, PA.

1982-present - Senior Scientist, Neurological Sciences Institute, Good Samaritan Hospital and Medical Center, Portland, OR.

HONORS AND FELLOWSHIPS

A.B. with High Honors; Phi Beta Kappa; Psi Chi; Beginning Knapp Fellow; NSF Cooperative Fellow; Fogarty Senior International Fellow; 1980-1981; Invited Speaker, Satellite Symposium on Sensory Processing in the Dorsal Horn,

Keszthely, Hungary, July 9-12, 1980; Invited Speaker, Symposium on "Abnormal sensations following peripheral nerve injury: Possible mechanisms", American Pain Society, Miami, Oct. 29, 1982.

ORGANIZATIONS

American Association of Anatomists, Society for Neuroscience, Member of the Council of the Philadelphia Neuroscience Society, 1977-1982 (Secretary, 1979-1980, Vice President 1981-1982), Member of the Chapters Committee of the Society for Neuroscience.

CONSULTING

Board of Scientific Counselors of the National Institute of Dental Research, 1980-1984

Reviewer of NSF Research Grant Applications and Manuscripts submitted to the Journal of Neurophysiology, Journal of Anatomy, Experimental Neurology and The Behavioral and Brain Sciences.

Special reviewer, NIH Individual National Research Service Awards, Behavioral and Neurosciences - 1 Study Section, 1982

RECENT REPRESENTATIVE PUBLICATIONS

1973 - Pubols, Lillian M., and Pubols, B.H. Modality composition and functional characteristics of dorsal column mechanoreceptive afferent fibers innervating the raccoon's forepaw. J. Neurophysiol. 36: 1023-1037.

1976 - Pubols, B.H., Pubols, L.M., DiPette, D.J. and Sheely, J.C. Opossum somatic sensory cortex: A microelectrode mapping study. J. Comp. Neurol. 165: 229-245.

1976 - Pubols, B.H. and Pubols, L.M. Coding of mechanical stimulus velocity and indentation depth by squirrel monkey and raccoon glabrous skin mechanoreceptors. J. Neurophysiol. 39: 733-837.

1977 - Pubols, L.M. and Leroy, R.F. Orientation detectors in the primary somatosensory neocortex of the raccoon. Brain Research 129: 61-74.

1977 - Pubols, L.M., Leroy, R.F. and Pubols, B.H. Response of raccoon SI neurons to temporally distributed tactile stimuli applied to the forepaw. Brain Research 132: 558-561.

1979 - Pubols, B.H. and Pubols, L.M. Variations in the fissural pattern of the cerebral neocortex of the spider monkey (Ateles). Brain Behav. Evol. 13: 241-252.

1980 - Pubols, L.M. and Goldberger, M.E. Recovery of function in the dorsal horn following partial deafferentation. J. Neurophysiol. 43: 102-117.

1981 - Brenowitz, G.L. and Pubols, L.M. Increased response to sural nerve input in the dorsal horn following chronic spinal cord hemisection. Brain Research 208: 421-425.

1981 - Brenowitz, G.L. and Pubols, L.M. Increased receptive field size of dorsal horn neurons following chronic spinal cord hemisection in cats. Brain Research 216: 45-59.

1981 - Pubols, L.M. and Brenowitz, G.L. Maintenance of dorsal horn somatotopic organization and increased high threshold response after single root or spared root deafferentation in cats. J. Neurophysiol. 47: 103-112.

1981 - Pubols, L.M. and Brenowitz, G.L. Alteration of dorsal horn function by acute and chronic deafferentation. In Sensory Processes in the Dorsal Horn, A.G. Brown and M. Rethelyi (eds.), Scottish Academic Press, pp. 319-328.

1982 - Pubols, B.H. and Pubols, L.M. Magnitude scaling of displacement and velocity of tactile stimuli applied to the human hand. Brain Res. 233: 409-413.

1982 - Pubols, B.H. and Pubols, L.M. Receptor discharge and mechanical properties of glabrous skin. Fed. Proc. (in press).

- Brown, A.G., Brown, P.B., Fyffe, R.E.W. and Pubols, L.M. Effects of deafferentation on spinocervical tract neurons in the cat. J. Physiol. (accepted for publication).

- Brown, A.G., Brown, P.B., Fyffe, R.E.W. and Pubols, L.M. Responses of post-synaptic dorsal column neurons in the cat. J. Physiol. (accepted for publication).

Dr. BARMACK. I'm Dr. Barmack and I'm the chairman of the Neurological Sciences Institute, and I'll try to summarize the testimony. And then I'm sure Dr. Pubols and Dr. Black would be happy to answer your questions.

I want to preface my remarks with an observation that a theme has cropped up, a repeated theme, during the testimony of previous individuals and raised by Senator Domenici: How is it that you're able to encourage young people to enter the field of scientific investigation?

And I think what I would like to talk about is an alternative model because in academic institutions the necessity is to teach. The demographics, as I'm sure you are aware, suggest that there will be a declining enrollment. That means there are fewer teaching positions for outstanding scientists coming up through the system. And in order for these postdoctoral people to find jobs and to encourage young people to enter the field, there must be research positions available for them to fill in which they can use the talents that they've developed as students and undergraduates and graduate students and postdoctoral fellows.

And the Neurological Sciences Institute about which I'll make a few statements is a possible alternative means of allowing investigators to want to spend full time doing reseach and give them the opportunity to do it. The Neurological Sciences Institute was established at Good Samaritan Hospital by the administration there. They had four objectives? One was in order to achieve preeminence as a tertiary care center for the referral of patients with very difficult diseases to cure, they had to have a basic research program. A basic research program was essential to attract high-quality clinical chiefs to the hopsital.

A second objective, in developing a basic research program, was that a basic research program could provide a necessary continuing education for interns, residents, special fellows, postdoctoral fellows.

A third objective was that a collection of very good basic scientists provides a technical resource for the increasing use of very sophisticated technical equipment in most medical settings.

And a fourth objective, in establishing a broad base research program, was that such a research program in close collaboration with clinical expertise might suggest new ways to diagnose disease and cure disease.

Now we're lucky at the Neurological Sciences Institute in that we have 16 scientists at work, each affiliated with a separate clinical department: Neurology, neuro-otology, ophthalmology, physical medicine, and rehabilitation. And each of these scientists has a basic research laboratory in our institute, and each scientist is also a member of a clinical department.

Now at the risk of angering my colleagues at the Neurological Sciences Institute, I want to focus on just a few of the discoveries that have been made at our institute and to show you how this blend of basic science expertise and clinical skills benefits both the medical community in general, and in particular the medical community here in Portland, and the citizens of Oregon.

A number of us have research interest in the vestibular system. Now as you know the vestibular system is that part of the nervous system concerned with telling your brain how your body is moving. The obvious dysfunction of the vestibular system is dizziness. A number of us have studied the vestibular system at the very basic level: what neurons are involved and in coding what messages; how the semicircular canals work; what parts of the brain are involved in creating sensory signals and motor commands related to vestibular information.

One of our colleagues, Dr. Lewis Nashner, has been involved in designing a platform on which human subjects are capable of standing most of the time. But the platform can be moved in such a way that it takes advantage of vestibular information, visual information, and information from the feet. It can play off these various classes of information against each other. By using this platform uniquely designed by Dr. Nashner, it's been possible for Dr. Nashner to describe how vestibular information is processed in normal human subjects; and in collaboration with Dr. Owen Black he has been able to use this platform to carefully screen and diagnose cases of vestibular disorders.

Now, because the Neurological Sciences Institute is at Good Samaritan Hospital, it was possible for the hospital to recruit Dr. Black, a skilled clinician, sitting at my left. And because he's recruited here, he was able to extend his collaboration with Dr. Nashner. The consequence of this collaboration is a very improved diagnostic technique which, with the aid of support from National Institutes of Health special small business award, has now become a platform which can be designed in a simple enough manner so that it can be sold to other institutions throughout the world. And in essence, a small business has been created by some very fundamental research sponsored by the National Institutes of Health.

This research has obvious benefits for the patients in Oregon and potentially throughout the world.

My own research does not touch on patients with clinical disorders directly; but I must say the influence of this close collaboration between basic science and clinical investigation was brought home to me very dramatically recently when my next door neighbor came over to me—who's a senior citizen, on Social Security—came over and told me how much better she's feeling lately. She doesn't fall anymore. I said, "Well, I didn't know you fell anyway." Well, she was falling all the time especially at night; and she had gone from doctor to doctor. The first doctor she went to told her that it was a problem that all old age people have.

The second doctor she went to told her it was all in her head. The third doctor she went to told her that she has to be watching what she's drinking. The fourth doctor she went to was Owen Black, sitting at my left; and she was diagnosed—I have not discussed it with Dr. Black—but she probably has something like hydrops.

He was able to give her some pills, restore balance between fluids in the inner ear; and as a consequence, she doesn't fall anymore. I think

that's a significant improvement and an immediate improvement in the quality of health care delivered to the citizens of Oregon.

And this improvement of health care is a consequence of some very good basic research done at a number of different levels at the Neurological Sciences Institute.

Seated at my right is Dr. Lillian Pubols. She does basic research on mechanisms of spinal degeneration and regeneration. And it has obvious implications for patients suffering from spinal trauma.

Behind me, her husband, Dr. Benjamin Pubols, was one of the first recipients of the Jacob Javits investigator awards, the first recipient in Oregon. A 7-year award which carries over 1 million dollars' worth of funding given to distinguished scientists whose research, peer reviewed, is judged to be of extremely high merit.

Also in the room is Dr. Alvin Eisner, a new investigator——

Senator HATFIELD. Could we have Dr. Pubols stand up so everybody can know there is the second part of the team.

Dr. BARMACK. They are a team at home; but I can assure you they are individuals at work.

Another investigator here from our institute is Dr. Alvin Eisner. Al does work in the fundamental mechanisms involved in vision—as Senator Hatfield knows, recently visiting the new Devers Eye Clinic, reinaugurated after 25 years. Dr. Eisner has been involved in vision research in both normal subjects and patients with retinal disease; and there are great prospects for his research in providing early diagnosis of certain retinal diseases; if treated early, these diseases can be halted if not reversed.

There are at least 10 other investigators in our institute which I have not mentioned and the time is too short to allow it.

How has this research at the Neurological Sciences Institute fulfilled the goals of the hospital? Well obviously we have recruited outstanding clinical chiefs so that Good Samaritan Hospital is preeminent in the areas of ophthalmology and neuro-otology. It is a regional referral base for the entire Pacific Northwest.

Scores of interns and residents have been trained—special residents, postdoctoral fellows. We have had, going through our institution, prospective scientists from the age of 5 to the age of 50. We have grade school children, 60 of them every summer, coming through our laboratories for a special course which is taught. The title of the course is "I'm Sensational," and it teaches about their senses.

We have students from local colleges every summer. We have special students sponsored by the Saturday Academy, a private science-dedicated organization to improving the quality of science instruction in the city of Portland. And we have students from the Talented and Gifted Program from the Portland public schools. We have postdoctoral fellows all going through the institute, all learning about what it means to be a scientist and what it means to be a good clinician.

How is the Neurological Sciences Institute funded? It's primarily through investigator initiated RO–1 research awards from the National

Institutes of Health. These, as you know, are extremely competitive. I sit on a panel. Dr. Black sits on a panel, which reviews such proposals each year. I sit on a panel for the Eye Institute; Dr. Black, I believe, for the Neurological and Communicative Disorders Institute.

Over 85 percent of our budget comes from Federal sources. Some other money comes from the Cerebral Palsy Foundation, the National Aeronautics and Space Administration, the National Science Foundation.

Some of our research, as Senator Hatfield is aware, is sponsored by the Oregon Lions Sight and Hearing Foundation. They contributed over $1.5 million to the construction of the building which he just visited last week. But in addition to that they have an annual commitment to paying the medical bills of indigent patients, and an annual commitment to supporting basic research in the State of Oregon on vision.

Scientific grantsmanship is, of course, an extremely competitive enterprise. A scientific proposal submitted to the National Institutes of Health has roughly a 1 in 3 chance of being funded. Now those are long odds if you look at an entire career which is dependent on getting continual funding.

But we are proud of our staff in that every member of our 16 member staff is fully funded on an RO–1 investigator initiated awards. I once calculated what the probability of that happening by chance was, and I can assure you it's an extremely large number.

The continued success of the Neurological Sciences Institute rests on four factors. One is our ability to continue to do meritorious research, meritorious research as perceived and reviewed by our colleagues.

Two: We must serve as an educational resource for the community, and a technical resource for the hospital medical center and the greater medical community.

Three: There must be Federal funding available.

Four: We must develop continued affiliations with other private organizations within the city of Portland and the State of Oregon.

My colleagues at the table and my colleagues in the audience and my colleagues at the Neurological Sciences Institute are grateful to have the opportunity of testifying before your committee; and we join the rest of the scientists who have already testified in expressing our warm appreciation for your efforts on the behalf of science. And we sincerely appreciate your efforts today. Thank you.

Senator HATFIELD. Thank you, Dr. Barmack. Senator Domenici, I wonder if maybe the other two doctors would like to make some brief comments.

Dr. Barmack, why don't you share with Senator Domenici a little bit about the role that you play with NASA and the opening of the institute with one of the astronauts, and the specific relationship that exists there.

Dr. BARMACK. Well, I suppose I shouldn't be so coy as to use the term spinoff, but the second priority health care problem in space is

space motion sickness, because the astronaut must live in an environment—and expecially when he goes outside the space craft—he must live in an environment into which he cannot vomit. And if he were to do that, it would have obvious consequences.

About 50 percent of the astronauts who go into space now become motion sick. So our role in working with NASA is to first of all help to prevent the problem, but second of all to better understand it so that we can deal with it on an individual basis.

I might add that the research that led to my involvement of the NASA program was originally funded by NIH. It was a direct outcome of an interest that I had in the vestibular system, the system that is responsible for the motion sickness. And I had no earthly idea when I started that it would lead to NASA research. So I would like to echo the comments that were made here relating the importance of funding fertile young minds for fertile young efforts that lead to unbelieveable consequences and important health care delivery methods.

Senator HATFIELD. Dr. Pubols, would you like to make some more specific comments?

Dr. PUBOLS. I really have no formal remarks prepared; but I would just like to second what Dr. Barmack said about the unique arrangement that we have at Good Samaritan Hospital for encouraging basic science and clinical collaboration where we're all members of clinical departments.

In my own case where I'm interested in the effects of injury on the spinal cord; I feel I must keep in close touch with the clinicians who deal with this problem every day, and their input is very important to me research. What the patients can tell them and what they can tell me about the patients give me new ideas to go back into the laboratory, and what I can tell them is of benefit to them I hope. And ultimately we can try to do something about this problem.

Senator HATFIELD. Do you have any questions, Senator Domenici?

Senator DOMENICI. Just a couple. Dr. Barmack, your role in the institution in Good Samaritan overall is what? What are you?

Dr. BARMACK. I'm the chairman of the Neurological Sciences Institute.

Senator DOMENICI. Now I don't think you should be the least bit defensive and maybe you started a little defensive at first, but you're a different model for research as compared to what we've heard. I think we're going to have to have a lot of variety, and I think that's exciting that you're doing similar research to the more pure institution that doesn't necessarily take care of patients on a daily basis as a hospital, and as compared with the NIH.

But let me ask you this: Are we in touch with you all sufficiently to make sure that as we change the rules about the costs of hospital care through medicare and medicaid and the like, that we aren't minimizing the ability to continue to have your kind of institute related to a hospital?

Dr. BARMACK. No; I don't think that would happen. I'm sorry I seemed defensive at first. That was not my intention. And I wouldn't characterize our research as unpure. I merely meant it to characterize the uniqueness of our institution where people are given free reign to work on the problems that they choose of a very basic nature, but they are housed in close proximity to clinicians at work on obviously topics of clinical importance.

And because the two groups are housed close together and members of the same department, we feel there is a better interaction and a better appreciation for the role of basic science research and its ability to lead to breakthroughs in medicine.

Obviously there's a great revolution taking place in the delivery and the compensation for medical care. But our institution derives just a nominal amount of money—and up until the last year not a single dollar spent on patient care, also made it into research. So I would guess that if the priorities of the Federal Government were to enhance the amount of money available for investigator initiated awards and that money was distributed on a competitive basis, on a peer review basis, that members of our institution would be extremely gratified because we feel we can compete no matter where we are.

Senator DOMENICI. Thank you, Mr. Chairman.

Senator HATFIELD. Thank you. I would like to make just one closing observation. First I would like to again express my deep appreciation to each one of the witnesses today. Senator Domenici as well as myself have sat through many hearings; and I often thought I would like to have a graph of quality of testimony through a hearing. I'm sure that Senator Domenici would agree that in his Budget Committee and other committees that he serves on, like my own committee assignments, that that graph would indicate this kind of result:

I think today has been an exceptional hearing compared to most of the hearings that I've sat through in that we started high and we stayed high and we ended high. It would have been a graph like this [indicating]. Not one like this [indicating], as far as the quality of the testimony and the witness are concerned. We have been blessed today. I have thought, my goodness, we're going to be here probably 3 hours this afternoon. It seems like it's only been about an hour because of the quality of the testimony, the quality of the people who have been here. And so I'm very grateful, speaking on behalf of Senator Domenici and myself both, that the people who have taken the time to come and prepare their testimony and delivered it in great eloquence, it's all contributed to a very special hearing.

We'll be happy to share this hearing record with all of you, as we will keep the hearing record open for 2 weeks for any additional testimony that any person or group may wish to submit.

Once again, Dr. Goldstein, we particularly want to thank you for coming from Washington for this specific hearing. You have added great status to the hearing as well as eloquence of testimony.

Senator Domenici?

Senator DOMENICI. Let me say to all of you how pleased I am to be here with your Senator. He's one of my best friends. That doesn't mean that I would come all the way to Oregon for him every other day, but it's great to be here today and to participate in this hearing. He's going to have to reciprocate and walk through northern New Mexico tomorrow. And we're going to walk some ditches and look at some waterways, and we're not going to get to hear as many exciting words.

But let me suggest to all of you and to our distinguished chairman, what we're really saying and what you make me appreciate is basically that we have some magnificent people in this country; and for the areas we're talking about right now during this whole hearing, we have to continue to maintain a level of consistency with reference to funding. But we have to keep very alive the individual freedom and diversity that is taking place so that we can't use the NIH as some central bureaucracy of medical research and expect to find it producing what we're getting with the diversity that's occurring here because you're going to be able to rival some of their expertise and Nobel-type scientists here in your institution. And you're going to have another model and we're going to help fund you.

And it's the challenge that comes with the freedom; but without the consistency and level of funding clearly we're going to get a much inferior result or a much delayed result. In either case that's not very good for people which we ought to be trying to help. So I'm very pleased that you contribute to my feelings about this and to my education, and I thank you for having me here, Mr. Chairman.

CONCLUSION OF HEARING

Senator HATFIELD. Thank you, dear friend. Any further comments? If not, the committee will stand in recess until the call of the Chair.

[Whereupon, at 4:25 p.m., Friday, August 24, the hearing was concluded, and the subcommittee was recessed subject to the call of the Chair.]

○